EXTRACRANIOFACIAL ANOMALIES IN CRANIOFACIAL MICROSOMIA: RETROSPECTIVE ANALYSIS OF 991 PATIENTS

Short running title: Extracraniofacial anomalies in CFM

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ABSTRACT

Craniofacial microsomia (CFM) is characterized by a unilateral or bilateral underdevelopment of the facial structures arising from the first and second pharyngeal arches, but extracraniofacial anomalies may be present. This retrospective study provides an overview of the prevalence and types of extracraniofacial anomalies in patients with CFM and studied the characteristics of patients with CFM and extracraniofacial anomalies. All patients diagnosed with CFM seen in four craniofacial centers were included. Patients charts were reviewed and data on patient characteristics and extracraniofacial anomalies were extracted. A total of 991 patients were included. Forty-six percent of the patients had extracraniofacial anomalies. The prevalence of extracraniofacial anomalies in all various tracts was: vertebral 28%, central nervous system 11%, circulatory system 21%, respiratory tract 3%, gastro-intestinal tract 9%, and urogenital tract 11%. Patients with an extracraniofacial anomaly had a higher risk for having additional extracraniofacial anomalies in other tracts compared to patients without extracraniofacial anomalies. The prevalence of extracraniofacial anomalies was greater in patients with bilateral CFM, a more severe mandibular deformity or facial nerve or soft tissue deformity. Patients with CFM should be screened for extracraniofacial anomalies by psychical examination with specific attention aimed at the circulatory, renal, and neurological tracts. Diagnostically, electrocardiography, echocardiogram, spine radiography and a renal ultrasound should be obtained in patients at risk for extracraniofacial anomalies.

LEVEL OF EVIDENCE

Level III: Retrospective cohort study

INTRODUCTION

The first and second pharyngeal arches give rise to various facial structures such as the mandible, maxilla, zygoma, ears, facial nerves and/or facial soft tissues (1). In patients with craniofacial microsomia (CFM) the structures arising from these arches may be underdeveloped or absent. The exact origin of this congenital disorder is yet unknown, although various theories have been proposed. A disruption in the development of the first and second pharyngeal arches during the first six weeks of development is potentially the cause of CFM (2-4). An error in migration of neural crest cells has found to form craniofacial anomalies as found in patients with CFM (5, 6). The clinical spectrum varies from a mild to severe phenotype and can be unilateral or bilateral (3, 7, 8). Although the ears may be underdeveloped or absent, isolated microtia is generally not regarded to be CFM (4).

Various classification systems have been proposed to categorize patients with CFM (6, 9-14). The Pruzansky-Kaban classification is based on radiographic evaluation of the underdevelopment of the mandible and temporomandibular joint, and is graded from mild to severe in type I, -IIA, -IIB, or –III (11, 15, 16). An alternative model, the O.M.E.N.S-plus classification, focuses on the level of underdevelopment of the Orbit (O), Mandible (M), Ears (E), Facial Nerve (N), Soft Tissue (S), and the presence of extracraniofacial anomalies (6, 9).

These extracraniofacial anomalies may be present in up to 55% of the patients with CFM and may occur in the vertebral column and ribs, the central nervous system (CNS), the circulatory-, respiratory-, gastro-intestinal-, and/or urogenital tract (6, 17-19). According to previous literature, the prevalence of extracraniofacial anomalies in CFM varies from 2% to 79% (6, 17, 19). Patients with a higher O.M.E.N.S. score are thought to have increased incidence of extracraniofacial anomalies (6). Additionally, patients with an extracraniofacial anomaly have a higher incidence of additional extracraniofacial anomalies in other tracts (18, 20). To recognize and potentially treat these anomalies in an early state, clinicians should be aware of the potential extracraniofacial anomalies in CFM. However, no literature is available on which patients with

CFM are at an increased risk of having extracraniofacial anomalies and should be screened for these anomalies.

The aim of this study is to provide an overview of the extracraniofacial anomalies found in CFM and to determine which patients with CFM have an increased likelihood of having extracraniofacial anomalies.

METHODS

Subjects and Data collection

A global multicenter retrospective study was initiated at the craniofacial centers of Erasmus University Medical Center (EMC), Rotterdam, The Netherlands; Great Ormond Street Hospital (GOSH), London, United Kingdom; Boston Children's Hospital (BCH), Boston, United States of America, and The Hospital for Sick Children, Toronto, Canada. This study was approved by the Institutional Review Boards (Rotterdam: MEC-2012-248; London: 14DS25; Boston: X05-08-058; Toronto: 1000053298).

All patients diagnosed with CFM seen in these craniofacial centers were included for further analyses. Since CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic x-rays and/or CT head, were included in this study. Patients in which the diagnosis of CFM could not be confirmed with the use of clinical and/or radiographic imaging and patients with isolated microtia were excluded. Patient charts of all included patients were reviewed and data on age, sex, affected side, Pruzansky-Kaban classification, O.M.E.N.S. classification and the presence of extracraniofacial anomalies was extracted. Patients with extracraniofacial anomalies were further analyzed. For each extracraniofacial anomaly present, data on type, location and date of diagnosis of the anomaly were noted.

The O.M.E.N.S classification system was used to grade the facial malformations in CFM patients (9, 21). The severity of the mandibular hypoplasia was determined by using the Pruzansky classification modified by Kaban et al. (11, 15, 16). In patients with bilateral CFM both facial- and mandibular sides were scored, but only the scores of the most affected side of the face were used for analysis. In this study, the M-score of the O.M.E.N.S. score was based on the Pruzansky-Kaban classification scored on radiography as proposed by Vento et al.(9) and not on clinical photography as suggested in the PAT-CFM developed by Birgfeld et al (21).

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson's Chi-square Test for Independence. Fisher's Exact Test was used when the assumptions for Pearson-Chi square test were violated (i.e. expected count less than 10). A univariate binary logistic regression model was used to evaluate the association between the extracraniofacial anomalies, and between the O.M.E.N.S and Pruzansky score. A P-value of <.05 was considered to be statistically significant.

RESULTS

Characteristics of patient population

A total of 1132 patients with CFM were diagnosed between all four craniofacial centers. Following exclusion of 141 patients due to diagnostic inconclusiveness or isolated microtia, 991 patients were included for further analyses. Fifty-five percent (n=527) was male and 47% (n=464) was female. Most patients had unilateral CFM (n=827), 177 had bilateral CFM and in 47 the affected side was unknown. Patient characteristics are shown in table 1.

Characteristics of patients with extracraniofacial anomalies

Of the 991 patients included in this study, 46 % (n=462) of patients were diagnosed with at least one extracraniofacial anomaly. The number of extracraniofacial anomalies per patient varied and could by present in various tracts simultaneously, as shown in figure 1. Fifty-five percent of the patients with an extracraniofacial anomaly was male (n=252) and forty-five percent was female (n=210). Seventy-nine percent (n=367) of the patients with an extracraniofacial anomaly had unilateral CFM, 17 % (n=79) had bilateral CFM and of 4% (n=16) of the patients with an extracraniofacial anomaly the affected side was unknown. The prevalence of extracraniofacial anomalies was found to be significantly higher in patients with bilateral CFM than in patients with unilateral CFM *(Pearson's χ^2 (df 1)=22.03, Odds ratio=2.61, 95% CI 1,7-3,9, P-value=<0.0001)*.

Types of extracraniofacial anomalies

The various types of extracraniofacial anomalies diagnosed in our study population are shown in table 2. Vertebral anomalies were most frequently seen, in 28% of the patients with CFM (n=275). Most seen anomalies were scoliosis, block vertebrae, hemivertebrae, and anomalies of the ribs. Anomalies of the central nervous system were reported in 11% of the patients with CFM (n=105). Hydrocephaly, ventriculomegaly, intracranial cysts, and Arnold Chiari malformation were mostly seen. Of the 28 patients with anomalies of the spinal cord, such as spina bifida or tethered cord, 27 patients had vertebral anomalies too *(Odds ratio=77.84, P-*

value=<0.001). Anomalies of the circulatory system were present in 21% of the patients with CFM (n=205). Mostly seen were ventricular or atrial septal defects, patent ductus arteriosus, and anomalies of the valves. Three percent of all patients with CFM (n=29) had an anomaly of the respiratory tract (n=14), such as laryngo- or tracheomalacia, or lung hypoplasia. Of these 29 patients with a respiratory anomaly, 14 patients had a cardiac anomaly too. Anomalies of the gastro-intestinal tract were present in 9% of the patients (n=89). Although the variety of anomalies is large, inguinal hernia, imperforate anus, esophageal atresia, and umbilical hernia were mostly seen. Urogenital anomalies occurred in 11% of the patients (n=108). Mainly, renal aplasia, undescended testis, and hydronephrosis were observed.

Correlations extracraniofacial anomalies

Table 3. shows the statistical analysis of which patients with an extracraniofacial anomaly had a higher incidence of additional extracraniofacial anomalies in other tracts. Patients with an extracraniofacial anomaly in any tract were found to have a significant higher risk for additional extracraniofacial anomalies in other tracts, except for anomalies of the respiratory tract. The correlation strength for the presence of extracraniofacial anomalies in different tracts varied from a Pearson's χ^2 (df 1) of 88.72 and an odds ratio of 6.64 (p=<0.001) for vertebral anomalies and anomalies of the central nervous system, to a Pearson's χ^2 (df 1) of 15.53 and an odds ratio of 2.33 (p=<0.001) for circulatory anomalies and anomalies of the urogenital tract. Anomalies of the respiratory tract were observed in fewer patients than anomalies of other tracts and were positively correlated with the presence of anomalies of the circulatory system *(Odds ratio=3.77, P-value=0.001)* and gastro-intestinal tract *(Odds ratio=4.96, P-value=0.001)*.

The O.M.E.N.S. score was used to examine a possible correlation between the facial malformations in CFM and the presence of extracraniofacial anomalies. Of various patients, data of components of the O.M.E.N.S. score was missing: in 217 patients the Orbit score was unknown, in 328 patients the Mandible score was unknown, the Ear score was unknown in 242 patients, in 598 patients the Nerve score were not available, and the Soft Tissue score was unknown in 233 patients.

The statistical analysis of the correlation of the O.M.E.N.S. score with extracraniofacial anomalies is displayed in table 4. A higher incidence of extracraniofacial anomalies was observed in patients with a higher Mandible score, Nerve score*s*, or Soft Tissue score of the O.M.E.N.S. score. This significant correlation was not observed in patients with a higher Orbit or Ear score. A positive correlation between the Orbit score and extracraniofacial anomalies was solely present for vertebral anomalies and not for extracraniofacial anomalies in other tracts. The Ear score was positively correlated with circulatory anomalies and not with extracraniofacial anomalies in other tracts. The mandible score had the highest correlation strength for the presence of extracraniofacial anomalies compared to other components of the O.M.E.N.S. score (Pearson's r=0.331, Odds ratio=1.39, P-value=<0.001).

DISCUSSION

The aim of this study was to present an overview of the extracraniofacial anomalies in CFM and to determine which patients with CFM have an increased likelihood for having these anomalies. A total of 991 patients were included, with a male to female ratio of 1.14:1, which is in line with previous literature (22). Eighteen percent of the patients were diagnosed with bilateral CFM, which is higher than the 13,6% reported by meta-analysis by Xu et al (22).

Forty-six percent of all patients studied (n=462) were diagnosed with extracraniofacial anomalies. The extracraniofacial anomalies were observed in all various tracts, such as the vertebral column (in 28%), central nervous system (in 11%), circulatory (in 21%), gastro-intestinal (in 9%), and urogenital (in 11%) tract, but were considerably scarce in the respiratory tract (in 3%). This may be due to a difference in the embryological development of these organs. The etiology of CFM is unknown, yet various theories have been proposed (2-4). Hereditary cases of CFM are known and when examining family members of patients with CFM with more detail for dysmorphologies, 45% of the family members tend to have some manifestation that could be part of CFM (23). Various genes have been proposed to cause CFM, but no single origin has been identified (4, 20). However, a recent genome-wide association study has identified a number of genetic loci associated with CFM that express neural crest genes (24). An alteration in the development of the first and second pharyngeal arches during the first six weeks of development appears to be the cause of CFM (3, 4). During these weeks the facial structures are formed by the first and second pharyngeal arches after neural crest cells migrated into these arches forming ectomesenchyme (25-27). A defect in the generation or migration of neural crest cells has been suggested to be the origin of the developmental deformities found in CFM (25-27). Abnormal migration of neural crest cells has been found to form the basis of craniofacial, vertebral, central nervous system, cardiovascular, and urogenital anomalies (5, 6, 28). The lungs are formed out of the primitive foregut and are further developed by epithelia, which is of endodermal descent, and mesenchymal cells (29). During development of the lung, neural crest cells play a role in the development of the intrinsic neurons which innervate the airway smooth muscles (30). Disturbing this process may originate in inadequate formation of the lungs. Although neural crest

cells play a role in the development of the respiratory tract, less evidence is available on a link between neural crest cells and anomalies in this tract. This may be the reason why less anomalies of the respiratory tract were found in our studied cohort compared to anomalies in other tracts.

The prevalence of extracraniofacial anomalies in CFM in our studied cohort is 46%, which is considerably higher than the incidence of 0,001%-2% in live births in the healthy population (31-33). The prevalence found in our studied population is similar to the 44% found by Rollnick et al. (19), but lower than the 55% reported by Horgan et al. (6) and the 69% by Barisic et al (17). This may be due to differences in patient selection, study characteristics and sample size. In the study by Rollnick et al. (n=294) 31% of the included patients had isolated microtia, which may have led to a lower prevalence of extracraniofacial anomalies in their studied population since these patients do not fit the criteria of CFM used in this study (19). The study by Horgan et al. (n=121) included patients with "hemifacial microsomia" without further specification of the clinical criteria used (6). Barisic et al. (n=269) included patients with microtia/ear anomalies and at least one major anomaly of the oculo-auriculo-vertebral spectrum (17). The prevalence of extracraniofacial anomalies found in our study may be higher since our study is retrospective and data are based on chart review. Thereby, not all extracraniofacial anomalies lead to clinical symptoms and may therefore remain undiagnosed. Although the actual prevalence remains uncertain, this large retrospective study shows extracraniofacial anomalies are common in CFM. Only a well-designed prospective study could comprehensively characterize extracraniofacial anomalies in CFM.

Horgan et al. found, by using the sum of the O.M.E.N.S. score, that patients with a higher O.M.E.N.S. score had a higher risk for extracraniofacial anomalies (6). In our studied cohort, patients with bilateral CFM, a higher Pruzanksy-Kaban score, and/or a higher Nerve, and/or Soft Tissue score on the O.M.E.N.S. scale had a significant higher incidence of extracraniofacial anomalies. Caron et al. and Tuin et al. found that deformities of the Orbit, Mandible, and Soft Tissue, which originate from the first pharyngeal arch, are significantly correlated with each other (18, 34). A correlation between the structures derived from the second pharyngeal arch as scored

in the Nerve and Ear score, and the Nerve and Soft Tissue score was also found (34). This study did not find a correlation between the presence of extracraniofacial anomalies and the O.M.E.N.S. score clusters as described by Caron et al. and Tuin et al. This could be due to a different, systemic pathophysiological mechanism compared to patients with isolated facial anomalies.

Patients with an extracraniofacial anomaly had a significant higher risk for additional extracraniofacial anomalies in other tracts compared to patients without extracraniofacial anomalies. This correlation was present in all various tracts these anomalies can occur in, except for the respiratory tract and vertebrae, and the respiratory tract and central nervous system. Tasse et al. found a significant correlation between genito-urinary anomalies and vertebral anomalies, but anomalies of the brain were not correlated with the presence other extracraniofacial anomalies in their studied cohort (10). The significant correlation between anomalies of the circulatory system and respiratory tract was also observed by Kumar et al. (35) but not by Barisic et al (17). Both studies did not observe a significant correlation between anomalies of the circulatory system and urogenital tract, as found in our study (17, 35).

Since our study is retrospective, it is uncertain whether patients with an extracraniofacial anomaly were assessed in more detail for the presence of additional anomalies. Therefore, a detection bias may be present. Nevertheless, this study shows that extracraniofacial anomalies are common in patients with CFM. Patients with CFM should be screened for potential harmful anomalies. Therefore, thorough physical examination should be performed in all patients with CFM. Anomalies of the circulatory system should be ruled out by cardiac evaluation using electrocardiography and/or echocardiogram in patients with a higher risk for extracraniofacial anomalies (33, 36). A renal ultrasound to diagnose urogenital anomalies in an early stage should be obtained in these patients as well (37). Neurological evaluation should be performed and if abnormal, an MRI of the brain and spine should be performed to rule out any anomalies (38, 39). If vertebral anomalies are suspected, standard upright posterior-anterior and lateral radiographs should be obtained (38, 40).

CONCLUSION

The prevalence of extracraniofacial anomalies in CFM in our studied cohort of 991 patients was 46%. Patients with bilateral CFM, and/or a high Pruzansky-Kaban score, or a high Nerve and/or Soft Tissue on the O.M.E.N.S. scale have a higher risk for extracraniofacial anomalies. Having extracraniofacial anomalies increases the risk for having additional extracraniofacial anomalies. All patients with CFM should be screened for extracraniofacial anomalies by a thorough physical examination with specific attention aimed at the circulatory, renal, and neurological tracts. Additionally, electrocardiography, echocardiogram, spine radiography and a renal ultrasound should be obtained in patients at risk for extracraniofacial anomalies.

Regarding the pathogenesis of CFM, the abundance of extracraniofacial anomalies in CFM patients and the strong correlation between them and with craniofacial (pharyngeal arch) defects suggests that the basis for this disorder lies with the neural crest cells. The fact that the pharyngeal arches are involved could be due to the fact the correct formation of these structures relies heavily on correct migration of neural crest cells during early embryonic development.

Table 1. Demographics for patients with and without extracraniofacial anomalies

		Extracraniofacial anomalies					
		Yes		No		Total	
Total		462	(47%)	529	(53%)	991	(100%)
Sex	Male	252	(48%)	275	(52%)	527	(53%)
	Female	210	(45%)	254	(55%)	464	(47%)
Laterality	Unilateral	367	(44%)	460	(56%)	827	(83%)
	Bilateral	79	(68%)	38	(32%)	117	(12%)
	Unknown	16	(34 %)	31	(66%)	47	(5%)
Affected side (UCFM)[#]	Right	199	(43%)	264	(57%)	463	(56%)
	Left	168	(46%)	196	(54%)	364	(44%)
Orbit*	0	183	(45%)	227	(55%)	410	(53%)
	1	69	(53%)	60	(47%)	129	(17%)
	2	53	(51%)	50	(49%)	103	(13%)
	3	41	(44%)	53	(56%)	94	(12%)
	4	24	(63%)	14	(37%)	38	(5%)
Mandible**[†]	0	0	(0%)	1	(100%)	1	(1%)
	1	63	(39%)	98	(61%)	161	(24%)
	2A	72	(42%)	100	(58%)	172	(26%)
	2B	89	(51%)	86	(49%)	175	(26%)
	3	97	(63%)	57	(37%)	154	(23%)
Ear*	0	45	(39%)	69	(61%)	114	(15%)
	1	51	(46%)	60	(54%)	111	(15%)
	2	56	(59%)	39	(41%)	95	(13%)
	3	193	(47%)	214	(53%)	407	(54%)
	4	14	(64%)	8	(36%)	22	(3%)
Nerve*	0	100	(44%)	126	(56%)	226	(57%)
	1	21	(46%)	25	(54%)	46	(12%)
	2	39	(59%)	27	(41%)	66	(17%)
	3	24	(69%)	11	(31%)	35	(9%)
	4	11	(55%)	9	(45%)	20	(5%)
Soft Tissue*	0	55	(46%)	65	(54%)	120	(16%)
	1	132	(41%)	193	(59%)	325	(43%)
	2	127	(52%)	116	(48%)	243	(32%)
	3	47	(67%)	23	(33%)	70	(9%)

UCFM = unilateral craniofacial microsomia ; [#]In unilateral cases of craniofacial microsomia ; *Orbit, Ear, Nerve, Soft Tissue score on the O.M.E.N.S. scale ; **[†]Mandible score based on Pruzansky-Kaban classification ; ^See Table 4. for statistical analysis

Figure 1. Percentage of patients with extracraniofacial anomalies in multiple tracts

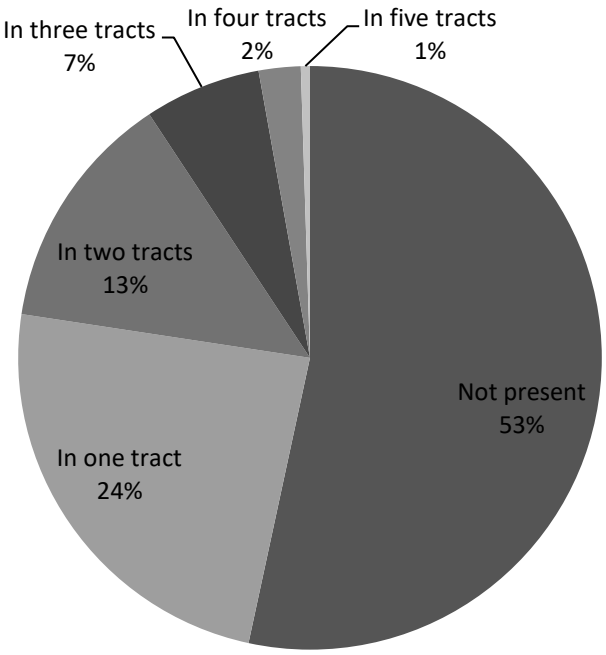

Table 2. Description of extracraniofacial anomalies

Vertebral anomalies (n=275)	Number patients	Central nervous system anomalies (n=105)	Number patients	Circulatory system anomalies (n=205)	Number patients	Respiratory tract anomalies (n=29)	Number patients	Gastro-intestinal tract anomalies (n=89)	Number patients	Urogenital tract anomalies (n=108)	Number patients
Scoliosis	162	Hydrocephaly	18	VSD	95	Laryngomalacia	15	Inguinal hernia	30	Renal aplasia	28
Block vertebrae	118	Ventriculomegaly	17	ASD	71	Lung hypoplasia	8	Imperforate anus	16	Undescended testis	15
Hemivertebrae	98	Intracranial cyst	17	Patent ductus arteriosus	42	Tracheomalacia	7	Esophageal atresia	11	Hydronephrosis	14
Not specified	49	Arnold Chiari	12	Valve anomaly	22	Tracheal stenosis	2	Umbilical hernia	11	Renal ectopia	10
Ribs fusion	27	Microcephaly	11	Tetralogy of Fallot	16	Absence of tracheal rings	1	Tracheoesophageal fistula	8	Hypospadias	10
Butterfly vertebrae	25	Intracranial lipoma	11	Artery malformation	15	Not specified	1	Intestines anomaly	6	Phimosis	9
Ribs aplasia	25	Spina bifida occulta	10	Pulmonic valve stenosis	13			Diaphragmatic hernia	5	Internal genital anomalies	7
Ribs extra	23	Hypoplastic corpus callosum	9	Arrhythmia	11			Meckel's diverticulum	4	Vesicoureteral reflux	6
Vertebral hypoplasia	18	Cerebral dysgenesis	9	Venous malformation	10			Intestinal malrotation	4	Bladder anomaly	6
Ribs hypoplasia	15	Not specified	8	Transposition of the great arteries	10			Polysplenia	3	External genital anomalies	6
Cervical ribs	12	Tethered cord	7	Ventricle anomaly	10			Diaphragm anomaly	3	Ureter anomaly	5
Lack of fusion vertebrae	12	Cerebral hemorrhage/infarction	8	Aortic anomaly	9			Liver anomaly	3	Hydrocele testis	5
Pectus deformity	12	Fatty filum terminale	5	TAPVR	6			Anal fistula	2	Renal hypoplasia	4
Cervical spine instability	7	Meningocele	5	Dextrocardia	4			Omphalocele	2	Duplex kidney anomalies	4
Rib anomaly n.s.	7	Cerebral hypoplasia	4	Situs inversus	1			Pyloric stenosis	2	Renal fusion	3
Occipitalization atlas	6	Encephalocele	4	Cardiomegaly	1			Situs ambiguous	1	Renal dysplasia	3
Atlanto-axial subluxation	4	Syringomyelia	4	Mesocardia	1					Renal anomaly n.s.	3
Vertebral agenesis	3	Macrocephaly	4	Not specified	1						
Sacralization	3	Intracranial mass n.s.	3								
Os odontoideum	2	Absent septum pellucidum	2								
Extra vertebrae	2										
Omo vertebral body	1										

n.s.: not specified, *TAPVR: Total anomalous pulmonary venous return

Table 3. Statistical analysis of the extracraniofacial anomalies in the various tracts

Extracraniofacial anomalies (number of patients)		Extracraniofacial anomalies (number of patients)					
		CNS (n = 105)	Circulatory (n = 205)	Respiratory (n = 29)	GI[#] (n = 89)	Urogenital (n = 108)	
Extracraniofacial anomalies (number of patients)	Vertebral (n = 275)	88.72	49.36	*	36.37	37.87	*Pearson's* χ^2
		6.64	3.01	2.17	3.67	3.41	Odds ratio
		0.30	0.22	-	0.19	0.20	Phi coefficient
		4.30-10.26	2.23-4.23	0.99-1.06	2.35-5.71	2.27-5.13	95% CI[†]
		<0.0001	**<0.0001**	0.055	**<0.0001**	**<0.0001**	P-value
	CNS (n = 105)		24.13	*	*	17.30	*Pearson's* χ^2
			2.82	0.62	3.49	2.83	Odds ratio
		-	0.16	-	-	0.13	Phi coefficient
			1.84-4.32	0.15-2.64	2.06-5.90	1.70-4.70	95% CI[†]
			<0.0001	0.76	**<0.0001**	**<0.0001**	P-value
	Circulatory (n = 205)			*	41.87	15.53	*Pearson's* χ^2
				3.77	4.05	2.33	Odds ratio
		-	-	-	0.21	0.13	Phi coefficient
				1.79-7.94	2.59-6.35	1.52-3.58	95% CI[†]
				0.001	**<0.0001**	**<0.0001**	P-value
	Respiratory (n = 29)				*	*	*Pearson's* χ^2
					4.96	2.71	Odds ratio
		-	-	-	-	-	Phi coefficient
					2.19-11.26	1.13-6.51	95% CI[†]
					0.001	**0.031**	P-value
	GI[#] (n = 89)					*	*Pearson's* χ^2
						4.13	Odds ratio
		-	-	-	-	-	Phi coefficient
						2.48-6.87	95% CI[†]
						<0.0001	P-value

[#]Gastro-Intestinal; *criteria for Pearson-Chi square test were not met, therefore the Fisher's Exact Test was used; [†]Confidence Interval

Table 4. Statistical analysis of the O.M.E.N.S. score in patients with extracraniofacial anomalies

	Extracranio facial anomalies (n = 462)	Vertebral anomalies (n = 275)	CNS anomalies (n = 105)	Circulatory anomalies (n = 205)	Respiratory anomalies (n = 29)	Gastro-intestinal anomalies (n = 89)	Urogenital anomalies (n = 108)	
Orbit*	0.086	0.120	0.022	0.088	0.130	0.051	0.005	*Pearson's r*
	1.09	1.13	1.02	1.09	1.14	1.05	1.01	Odds ratio
	0.97-1.22	1.00-1.28	0.85-1.23	0.95-1.25	0.84-1.54	0.87-1.27	0.84-1.12	95% CI[†]
	0.133	**0.049**	0.814	0.201	0.398	0.592	0.959	P-value
Mandible**	0.331	0.329	0.186	0.201	0.356	0.342	0.240	*Pearson's r*
	1.39	1.39	1.20	1.22	1.43	1.41	1.27	Odds ratio
	1.21-1.61	1.19-1.62	0.97-1.50	1.03-1.45	0.91-2.23	1.11-1.79	1.02-1.59	95% CI[†]
	<0.0001	**<0.0001**	0.094	**0.022**	0.118	**0.006**	0.033	P-value
Ear*	0.101	0.101	-0.014	0.161	0.121	0.143	-0.008	*Pearson's r*
	1.11	1.11	0.99	1.18	1.13	1.15	0.99	Odds ratio
	0.98-1.25	0.97-1.27	0.81-1.20	1.01-1.38	0.78-1.64	0.93-1.43	0.82-1.20	95% CI[†]
	0.10	0.146	0.889	**0.046**	0.524	0.189	0.934	P-value
Nerve*	0.233	0.238	0.107	0.188	0.048	0.292	0.236	*Pearson's r*
	1.26	1.27	1.11	1.21	1.05	1.34	1.27	Odds ratio
	1.07-1.49	1.07-1.50	0.89-1.39	1.01-1.45	0.49-2.26	1.05-1.70	1.02-1.57	95% CI[†]
	0.005	**0.005**	0.340	**0.045**	0.902	**0.017**	**0.033**	P-value
Soft Tissue*	0.300	0.203	-0.114	0.319	0.567	0.497	0.182	*Pearson's r*
	1.35	1.23	0.89	1.38	1.76	1.64	1.20	Odds ratio
	1.14-1.60	1.02-1.47	0.68-1.18	1.12-1.70	1.09-2.85	1.23-2.20	0.92-1.56	95% CI[†]
	0.001	**0.031**	0.421	**0.003**	**0.020**	**0.001**	0.173	P-value

*Orbit, Ear, Nerve, Soft Tissue score on the O.M.E.N.S. scale ; **Mandible score based on Pruzansky-Kaban classification; [†]Confidence Interval

REFERENCES

1. Grabb WC. The first and second branchial arch syndrome. Plast Reconstr Surg. 1965;36(5):485-508.
2. Poswillo D. Hemorrhage in development of the face. Birth Defects Orig Artic Ser. 1975;11(7):61-81.
3. Converse JM, Coccaro PJ, Becker M, Wood-Smith D. On hemifacial microsomia. The first and second branchial arch syndrome. Plast Reconstr Surg. 1973;51(3):268-79.
4. Birgfeld CB, Heike C. Craniofacial microsomia. Semin Plast Surg. 2012;26(2):91-104.
5. Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, et al. Retinoic acid embryopathy. N Engl J Med. 1985;313(14):837-41.
6. Horgan JE, Padwa BL, LaBrie RA, Mulliken JB. OMENS-Plus: analysis of craniofacial and extracraniofacial anomalies in hemifacial microsomia. Cleft Palate Craniofac J. 1995;32(5):405-12.
7. Poswillo D. The aetiology and pathogenesis of craniofacial deformity. Development. 1988;103 Suppl:207-12.
8. Gorlin RJ PJ. Syndromes of the head and neck. New York: McGraw-Hill. 1964:546-52.
9. Vento AR, LaBrie RA, Mulliken JB. The O.M.E.N.S. classification of hemifacial microsomia. Cleft Palate Craniofac J. 1991;28(1):68-76; discussion 7.
10. Tasse C, Bohringer S, Fischer S, Ludecke HJ, Albrecht B, Horn D, et al. Oculo-auriculo-vertebral spectrum (OAVS): clinical evaluation and severity scoring of 53 patients and proposal for a new classification. Eur J Med Genet. 2005;48(4):397-411.
11. Pruzansky S. Not all dwarfed mandibles are alike. Birth defects: Original Article Series. 1969;5:120-9.
12. Converse JM, Wood-Smith D, McCarthy JG, Coccaro PJ, Becker MH. Bilateral facial microsomia. Diagnosis, classification, treatment. Plast Reconstr Surg. 1974;54(4):413-23.
13. David DJ, Mahatumarat C, Cooter RD. Hemifacial microsomia: a multisystem classification. Plast Reconstr Surg. 1987;80(4):525-35.
14. Lauritzen C, Munro IR, Ross RB. Classification and treatment of hemifacial microsomia. Scand J Plast Reconstr Surg. 1985;19(1):33-9.

15. Kaban LB, Moses MH, Mulliken JB. Correction of hemifacial microsomia in the growing child: a follow-up study. Cleft Palate J. 1986;23 Suppl 1:50-2.

16. Kaban LB, Mulliken JB, Murray JE. Three-dimensional approach to analysis and treatment of hemifacial microsomia. Cleft Palate J. 1981;18(2):90-9.

17. Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, et al. Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe. Eur J Hum Genet. 2014;22(8):1026-33.

18. Caron C, Pluijmers BI, Wolvius EB, Looman CWN, Bulstrode N, Evans RD, et al. Craniofacial and extracraniofacial anomalies in craniofacial macrosomia: A multicenter study of 755 patients. J Craniomaxillofac Surg. 2017;45(8):1302-10.

19. Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO. Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet. 1987;26(2):361-75.

20. Beleza-Meireles A, Hart R, Clayton-Smith J, Oliveira R, Reis CF, Venancio M, et al. Oculo-auriculo-vertebral spectrum: clinical and molecular analysis of 51 patients. Eur J Med Genet. 2015;58(9):455-65.

21. Birgfeld CB, Luquetti DV, Gougoutas AJ, Bartlett SP, Low DW, Sie KC, et al. A phenotypic assessment tool for craniofacial microsomia. Plast Reconstr Surg. 2011;127(1):313-20.

22. Xu S, Zhang Z, Tang X, Yin L, Liu W, Shi L. The influence of gender and laterality on the incidence of hemifacial microsomia. J Craniofac Surg. 2015;26(2):384-7.

23. Rollnick BR, Kaye CI. Hemifacial microsomia and variants: pedigree data. Am J Med Genet. 1983;15(2):233-53.

24. Zhang YB, Hu J, Zhang J, Zhou X, Li X, Gu C, et al. Genome-wide association study identifies multiple susceptibility loci for craniofacial microsomia. Nat Commun. 2016;7:10605.

25. Snider TN, Mishina Y. Cranial neural crest cell contribution to craniofacial formation, pathology, and future directions in tissue engineering. Birth Defects Res C Embryo Today. 2014;102(3):324-32.

26. Johnson JM, Moonis G, Green GE, Carmody R, Burbank HN. Syndromes of the first and second branchial arches, part 1: embryology and characteristic defects. AJNR Am J Neuroradiol. 2011;32(1):14-9.

27. Twigg SR, Wilkie AO. New insights into craniofacial malformations. Hum Mol Genet. 2015;24(R1):R50-9.

28. Sulik KK, Johnston MC, Smiley SJ, Speight HS, Jarvis BE. Mandibulofacial dysostosis (Treacher Collins syndrome): a new proposal for its pathogenesis. Am J Med Genet. 1987;27(2):359-72.

29. Schittny JC. Development of the lung. Cell Tissue Res. 2017;367(3):427-44.

30. Freem LJ, Escot S, Tannahill D, Druckenbrod NR, Thapar N, Burns AJ. The intrinsic innervation of the lung is derived from neural crest cells as shown by optical projection tomography in Wnt1-Cre;YFP reporter mice. J Anat. 2010;217(6):651-64.

31. Shands AR, Jr., Eisberg HB. The incidence of scoliosis in the state of Delaware; a study of 50,000 minifilms of the chest made during a survey for tuberculosis. J Bone Joint Surg Am. 1955;37-A(6):1243-9.

32. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, Group ES. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. Eur J Med Genet. 2005;48(2):131-44.

33. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-900.

34. Tuin AJ, Tahiri Y, Paine KM, Paliga JT, Taylor JA, Bartlett SP. Clarifying the relationships among the different features of the OMENS+ classification in craniofacial microsomia. Plast Reconstr Surg. 2015;135(1):149e-56e.

35. Kumar A, Friedman JM, Taylor GP, Patterson MW. Pattern of cardiac malformation in oculoauriculovertebral spectrum. Am J Med Genet. 1993;46(4):423-6.

36. Allan LD, Sharland GK, Milburn A, Lockhart SM, Groves AM, Anderson RH, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol. 1994;23(6):1452-8.

37. MacEwen GD, Winter RB, Hardy JH. Evaluation of kidney anomalies in congenital scoliosis. J Bone Joint Surg Am. 1972;54(7):1451-4.

38. Chan G, Dormans JP. Update on congenital spinal deformities: preoperative evaluation. Spine (Phila Pa 1976). 2009;34(17):1766-74.

39. Basu PS, Elsebaie H, Noordeen MH. Congenital spinal deformity: a comprehensive assessment at presentation. Spine (Phila Pa 1976). 2002;27(20):2255-9.
40. Brand MC. Examination of the newborn with congenital scoliosis: focus on the physical. Adv Neonatal Care. 2008;8(5):265-73; quiz 74-5.