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Clinical Paper
Craniofacial Anomalies

Extracraniofacial anomalies in craniofacial microsomia: retrospective analysis of 991 patients

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Abstract. Craniofacial microsomia (CFM) is characterized by unilateral or bilateral underdevelopment of the facial structures arising from the first and second pharyngeal arches, but extracraniofacial anomalies may also be present. This retrospective study provides an overview of the prevalence, types, and characteristics of extracraniofacial anomalies in patients with CFM. All patients diagnosed with CFM seen at four craniofacial centres were included. The patient charts were reviewed and data on patient characteristics and extracraniofacial anomalies were extracted. Of the 991 patients included, 462 (47%) had extracraniofacial anomalies. The prevalence of extracraniofacial anomalies in the various tracts was as follows: vertebral 28%, central nervous system 11%, circulatory system 21%, respiratory tract 3%, gastrointestinal tract 9%, and urogenital tract 11%. Compared to patients without extracraniofacial anomalies, those with an extracraniofacial anomaly were at higher risk of having additional extracraniofacial anomalies in other tracts. 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 physical examination with specific attention to the circulatory, renal, and neurological tracts. Diagnostically, electrocardiography, echocardiography, spine radiography, and renal ultrasound should be performed for patients at risk of extracraniofacial anomalies.

Key words: craniofacial microsomia; oculo-auriculo-vertebral syndrome; hemifacial microsomia; Goldenhar syndrome; congenital anomalies; extracraniofacial anomalies; extracranial anomalies; retrospective studies; humans; branchial region; prevalence; screening; mandible; face; physical examination; attention; cardiovascular system; respiratory system; vertebral; spine; central nervous system; urogenital; gastrointestinal.

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The first and second pharyngeal arches give rise to various facial structures such as the mandible, maxilla, zygoma, ears, facial nerves, and 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 remains unknown, although various

theories have been proposed. A disruption in the development of the first and second pharyngeal arches during the first 6 weeks of development is potentially the cause of CFM[2–4]. An error in migration of neural crest cells has been found to form craniofacial anomalies as found in patients with CFM[5,6]. The clinical spectrum varies from a mild to a severe phenotype, and CFM 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 OMENS-plus classification, focuses on the level of underdevelopment of the orbit (O), mandible (M), ears (E), facial nerve (N), and soft tissue (S), and the presence of extracraniofacial anomalies[6,9].

These extracraniofacial anomalies may be present in up to 55% of patients with CFM and may occur in the vertebral column and ribs, the central nervous system (CNS), circulatory system, respiratory tract, gastrointestinal tract, and/or urogenital tract[6,17–19]. According to the previous literature, the prevalence of extracraniofacial anomalies in CFM varies from 2% to 79%[6,17,19]. Patients with a higher OMENS score are thought to have an 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 at an early stage, clinicians should be aware of the potential extracraniofacial anomalies in CFM. However, there are gaps in the literature on which patients with CFM are at increased risk of having extracraniofacial anomalies and should be screened for these anomalies.

The aim of this study was 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 multicentre retrospective study was initiated at the craniofacial centres of Erasmus University Medical Centre in The Netherlands (EMC, Rotterdam, The Netherlands), Great Ormond Street Hospital in the UK (GOSH, London, UK), Boston Children's Hospital in the USA (BCH, Boston, USA), and The Hospital for Sick Children in Canada (Toronto, Canada). This study was approved by the associated institutional review boards.

All patients diagnosed with CFM seen at these craniofacial centres were included for further analysis. Since CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic X-rays and/or computed tomography of the head, were included in this study. Patients in whom the diagnosis of CFM could not be confirmed with the use of clinical and/or radiographic imaging and patients with isolated microtia were excluded. The patient charts of all included patients were reviewed and data on age, sex, affected side, Pruzansky–Kaban classification, OMENS classification, and the presence of extracraniofacial anomalies were extracted. Patients with extracraniofacial

Table 1. Demographic characteristics of the patients with and without extracraniofacial anomalies.

	Extracraniofacial anomalies[d]				Total	
	Yes		No			
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)[a]						
Right	199	(43%)	264	(57%)	463	(56%)
Left	168	(46%)	196	(54%)	364	(44%)
Orbit[b]						
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[c]						
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[b]						
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[b]						
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[b]						
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.
[a]In unilateral cases of craniofacial microsomia.
[b]Orbit, ear, nerve, and soft tissue score on the OMENS scale.
[c]Mandible score based on the Pruzansky–Kaban classification.
[d]See Table 4 for the statistical analysis.

anomalies were further analyzed. For each extracraniofacial anomaly present, data on the type, location, and date of diagnosis of the anomaly were noted.

The OMENS classification system was used to grade the facial malformations in the CFM patients[9,21]. The severity of the mandibular hypoplasia was determined 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 OMENS score (mandible) 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 phenotypic assessment tool for CFM developed by Birgfeld et al.[21].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson χ^2 test for independence. Fisher's exact test was used when the assumptions for the Pearson χ^2 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 OMENS and Pruzansky score. A P-value of <0.05 was considered to be statistically significant.

Results

Characteristics of the patient population

A total of 1132 patients with CFM were diagnosed at the four craniofacial centres. Following the exclusion of 141 patients due to diagnostic inconclusiveness or isolated microtia, 991 patients were included for further analysis. Fifty-three percent (n = 527) were male and 47% (n = 464) were female. Most patients had unilateral CFM (n = 827), 117 had bilateral CFM, and the affected side was unknown for 47 patients. The characteristics of the patient population are shown in Table 1.

Characteristics of patients with extracraniofacial anomalies

Of the 991 patients included in this study, 462 (47%) were diagnosed with at least one extracraniofacial anomaly. The number of extracraniofacial anomalies per patient varied and these anomalies could by present in the same or other tracts simultaneously, as shown in Fig. 1. Fifty-five percent of the patients with an extracraniofacial anomaly were male (n = 252) and 45% were female (n = 210). Seventy-nine percent (n = 367) of the patients with an extracraniofacial anomaly had unilateral CFM and 17% (n = 79) had bilateral CFM; the affected side was unknown for 4% (n = 16) of the patients with an extracraniofacial anomaly. The prevalence of extracraniofacial anomalies was found to be significantly higher in patients with bilateral CFM than in patients with unilateral CFM (Pearson χ^2 (df 1) = 22.03, odds ratio (OR) 2.61, 95% confidence interval (CI) 1.7–3.9; $P < 0.0001$).

Types of extracraniofacial anomaly

The various types of extracraniofacial anomaly diagnosed in the study population are shown in Table 2. Vertebral anomalies were the most frequently seen anomalies in the patients with CFM (28%, n = 275); the predominant anomalies were scoliosis, block vertebrae, hemivertebrae, and anomalies of the ribs. Anomalies of the CNS 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 also had vertebral anomalies (OR 77.84; $P < 0.001$). Anomalies of the circulatory system were present in 21% of the patients with CFM (n = 205), with ventricular or atrial septal defects, patent ductus arteriosus, and anomalies of the valves being seen most frequently. Three percent of all patients with CFM (n = 29) had an anomaly of the respiratory tract, such as laryngomalacia or tracheomalacia, or lung hypoplasia. Of these 29 patients with a respiratory anomaly, 14 had a cardiac anomaly too. Anomalies of the gastrointestinal tract were present in 9% of the patients (n = 89). Although there was great variety in these anomalies, inguinal hernia, imperforate anus, oesophageal atresia, and umbilical hernia were those most often seen. Urogenital anomalies occurred in 11% of the patients (n = 108), and renal aplasia, undescended testis, and hydronephrosis were mainly observed.

Correlations of extracraniofacial anomalies

Table 3 shows the statistical analysis to determine which patients with an extracraniofacial anomaly showed a higher incidence of additional extracraniofacial anomalies in other tracts. Patients with an extracraniofacial anomaly in any tract were found to be at significantly higher risk of additional extracraniofacial anomalies in other tracts, except for anomalies of the respiratory tract. The strength of the correlation for the presence of extracraniofacial anomalies in different tracts varied from Pearson χ^2 (df 1) = 88.72 and OR 6.64 ($P < 0.001$) for vertebral anomalies and anomalies of the CNS, to Pearson χ^2 (df 1) = 15.53 and OR 2.33 ($P < 0.0001$) for circulatory anomalies and anomalies of the urogenital tract. Anomalies of the respiratory tract were observed in fewer patients than anomalies of the other tracts and were positively correlated with the

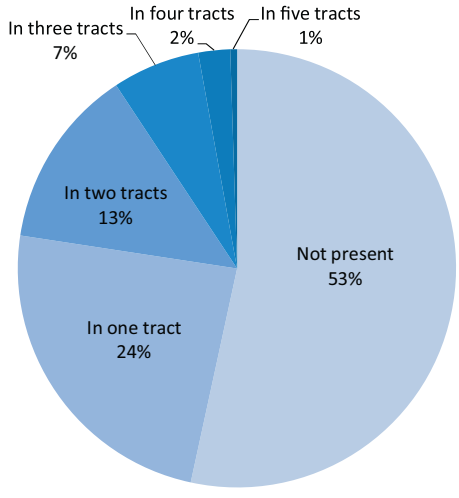

Fig. 1. Percentages of patients with extracraniofacial anomalies in multiple tracts.

Table 2. Description of the extracraniofacial anomalies found in the study population.

Vertebral anomalies ($n = 275$)	n[a]	CNS anomalies ($n = 105$)	n[a]	Circulatory system anomalies ($n = 205$)	n[a]	Respiratory tract anomalies ($n = 29$)	n[a]	Gastrointestinal tract anomalies ($n = 89$)	n[a]	Urogenital tract anomalies ($n = 108$)	n[a]
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	Oesophageal atresia	11	Hydronephrosis	14
NS	49	Arnold–Chiari	12	Valve anomaly	22	Tracheal stenosis	2	Umbilical hernia	11	Renal ectopia	10
Rib 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	NS	1	Intestinal anomaly	6	Phimosis	9
Rib aplasia	25	Spina bifida occulta	10	Pulmonary 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
Rib hypoplasia	15	NS	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 haemorrhage/ 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 NS	7	Cerebral hypoplasia	4	Situs inversus	1			Pyloric stenosis	2	Renal fusion	3
Occipitalization of the atlas	6	Encephalocele	4	Cardiomegaly	1			Situs ambiguous	1	Renal dysplasia	3
Atlanto-axial subluxation	4	Syringomyelia	4	Mesocardia	1					Renal anomaly NS	3
Vertebral agenesis	3	Macrocephaly	4	NS	1						
Sacralization	3	Intracranial mass NS	3								
Os odontoideum	2	Absent septum pellucidum	2								
Extra vertebrae	2										
Omovertebral body	1										

ASD, atrial septal defect; CNS, central nervous system; NS, not specified; TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect.
[a] Number of patients.

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 ($n = 29$)	Gastrointestinal ($n = 89$)	Urogenital ($n = 108$)	
Vertebral ($n = 275$)	88.72	49.36	[a]	36.37	37.87	Pearson χ^2
	6.64	3.01	2.17	3.67	3.41	OR
	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	[a]	[a]	17.30	Pearson χ^2
		2.82	0.62	3.49	2.83	OR
		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 ($n = 205$)	–	–	[a]	41.87	15.53	Pearson χ^2
			3.77	4.05	2.33	OR
			–	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 ($n = 29$)	–	–	–	[a]	[a]	Pearson χ^2
				4.96	2.71	OR
				–	–	Phi coefficient
				2.19–11.26	1.13–6.51	95% CI
				0.001*	0.031*	*P*-value
Gastrointestinal ($n = 89$)	–	–	–	–	[a]	Pearson χ^2
					4.13	OR
					–	Phi coefficient
					2.48–6.87	95% CI
					<0.0001*	*P*-value

CI, confidence interval; CNS, central nervous system; OR, odds ratio.
[a] Criteria for the Pearson χ.
[2] test were not met, therefore Fisher's exact test was used.
* significant.

presence of anomalies of the circulatory system (OR 3.77; P = 0.001), gastrointestinal tract (OR 4.91, P = 0.001), and urogenital tract (OR 2.71; P = 0.031).

The OMENS score was used to examine a possible correlation between the facial malformations in CFM and the presence of extracraniofacial anomalies. Data for various components of the OMENS score were missing for some of the study patients: the orbit score was unknown for 217 patients, the mandible score was unknown for 328 patients, the ear score was unknown for 242 patients, the nerve score was not available for 598 patients, and the soft tissue score was unknown for 233 patients.

The statistical analysis of the correlation between the OMENS score and extracraniofacial anomalies is displayed in Table 4. A higher incidence of extracraniofacial anomalies was observed in patients with a higher OMENS mandible score, nerve score, or soft tissue score. This significant correlation was not observed for patients with a higher orbit score or ear score. A positive correlation between the orbit score and extracraniofacial anomalies was present solely for vertebral anomalies and not for extracraniofacial anomalies in other tracts. The ear score was positively correlated with circulatory anomalies but not with extracraniofacial anomalies in the other tracts. Compared to the other components of the OMENS score, the mandible score had the highest correlation strength for the presence of extracraniofacial anomalies (Pearson's r = 0.331, OR 1.39; P < 0.0001).

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 of 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 the previous literature[22]. Twelve percent of the patients were diagnosed with bilateral CFM, which is in line with the 13.6% reported in a meta-analysis by Xu et al.[22].

Forty-seven percent of all patients studied (n = 462) were diagnosed with extracraniofacial anomalies. The extracraniofacial anomalies were observed in all of the various tracts, such as the vertebral column (in 28%), CNS (in 11%), circulatory system (in 21%), gastrointestinal tract (in 9%), and urogenital tract (in 11%), but were relatively scarce in the respiratory tract (in 3%). This may be due to a difference in the embryological development of these organs. The aetiology of CFM is unknown, but various theories have been proposed[2–4]. Hereditary cases of CFM are known and when examining family members of patients with CFM in greater detail for dysmorphology, 45% of the family members tend to have some manifestation that could be part of CFM[23]. Various genes have been proposed to be involved in the aetiology of

Table 4. Statistical analysis of the OMENS score in patients with extracraniofacial anomalies.

	Extracraniofacial anomalies ($n = 462$)	Vertebral anomalies ($n = 275$)	CNS anomalies ($n = 105$)	Circulatory anomalies ($n = 205$)	Respiratory anomalies ($n = 29$)	Gastrointestinal anomalies ($n = 89$)	Urogenital anomalies ($n = 108$)	
Orbit[a]	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	OR
	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[b]	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	OR
	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[a]	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	OR
	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[a]	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	OR
	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[a]	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	OR
	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

CI, confidence interval; CNS, central nervous system; OR, odds ratio.
[a] Orbit, ear, nerve, soft tissue score on the OMENS scale.
[b] Mandible score based on the Pruzansky–Kaban classification.
* significant.

CFM, but no single origin has been identified[4,20]. However, a recent genome-wide association study 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 6 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 migrate 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 shown to form the basis of craniofacial, vertebral, CNS, 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 lungs, neural crest cells play a role in the development of the intrinsic neurons that innervate the airway smooth muscles[30]. Disturbances to this process may result 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 fewer anomalies of the respiratory tract were found in the present study cohort compared to anomalies of the other tracts.

The prevalence of extracraniofacial anomalies in CFM in the study cohort was found to be 47%, which is considerably higher than the incidence of 0.001–2% in live births in the healthy population[31–33]. The prevalence found in the study population is similar to the rate of 44% reported by Rollnick et al.[19], but lower than the 55% reported by Horgan et al.[6] and 69% reported 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 patients included had isolated microtia, which may have led to a lower prevalence of extracraniofacial anomalies in their study population since these patients did not fit the criteria of CFM used in the present 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 the present study may be higher since this study was retrospective and data were based on chart review. Not all extracraniofacial anomalies lead to clinical symptoms and these may therefore remain undiagnosed. Although the actual prevalence remains uncertain, this large retrospective study showed that extracraniofacial anomalies are common in CFM. Only a well-designed prospective study will be able to comprehensively characterize extracraniofacial anomalies in CFM.

Horgan et al., using the sum of the OMENS score, found that patients with a higher OMENS score had a higher risk of extracraniofacial anomalies[6]. In the present study cohort, patients with bilateral CFM, a higher Pruzansky–Kaban score, or a higher nerve score or higher soft tissue score on the OMENS scale had a significantly 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 in the nerve and soft tissue score was also found[34]. The present study did not find a correlation between the presence of extracraniofacial anomalies and the OMENS 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 were at significantly higher risk of additional extracraniofacial anomalies

in other tracts compared to patients without extracraniofacial anomalies. This correlation was present for all of the various tracts in which these anomalies can occur, except for the respiratory tract and vertebrae, and the respiratory tract and CNS. Tasse et al. found a significant correlation between genitourinary anomalies and vertebral anomalies, but anomalies of the brain were not correlated with the presence other extracraniofacial anomalies in their study 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]. Neither study observed a significant correlation between anomalies of the circulatory system and urogenital tract, as found in the present study[17,35].

Since this study was 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, based on the large size of this multicentre cohort, it was possible to clearly demonstrate that extracraniofacial anomalies are common in patients with CFM. Patients with CFM should be screened for potential harmful anomalies. Therefore, a thorough physical examination should be performed for all patients with CFM. Anomalies of the circulatory system should be ruled out by cardiac evaluation using electrocardiography and/or echocardiography in patients at higher risk of extracraniofacial anomalies[33,36]. Renal ultrasound to diagnose urogenital anomalies at an early stage should also be performed for these patients[37]. A neurological evaluation should be conducted and if abnormal, magnetic resonance imaging 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].

In conclusion, the prevalence of extracraniofacial anomalies in this study cohort of 991 patients with CFM was 47%. Patients with bilateral CFM, and/or a high Pruzansky–Kaban score, or a high nerve score and/or soft tissue score on the OMENS scale are at higher risk of having extracraniofacial anomalies. The presence of extracraniofacial anomalies increases the risk of having additional extracraniofacial anomalies. All patients with CFM should be screened for extracraniofacial anomalies by thorough physical examination with specific attention to the circulatory, renal, and neurological tracts. Additionally, electrocardiography, echocardiography, spine radiography, and renal ultrasound should be performed for patients at risk of 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 of this disorder lies with the neural crest cells. The fact that the pharyngeal arches are involved could be due to the fact that the correct formation of these structures relies heavily on the correct migration of neural crest cells during early embryonic development.

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Competing interests

There are no conflicts of interest in relation to the materials or subject matter dealt with in this article.

Ethical approval

This study was approved by the relevant institutional review boards (Rotterdam: MEC-2012-248; London: 14DS25; Boston: X05-08-058; Toronto: 1000053298).

Patient consent

Not required.

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