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Research Paper
Craniofacial Anomalies

Ocular and adnexal anomalies in craniofacial microsomia: Type and prevalence in a multicentre cohort study

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Abstract. The aim of this multicentre retrospective cohort study was to describe and categorize the types of ocular and adnexal anomalies seen in patients with craniofacial microsomia (CFM) and to determine their prevalence. In addition, the relationship between the OMENS-Plus and Pruzansky–Kaban classification for each patient and the presence of ocular anomalies was investigated. A total of 881 patients with CFM from four different craniofacial centres were included. Data on ocular anomalies were gathered from the patient charts. Ocular anomalies were present in 33.9% of patients. Four subgroups of ocular and adnexal anomalies were identified. Type I ocular anomalies were present in 22.2%, type II in 19.0%, type III in 18.4%, and type IV in 14.5%. Several potentially preventable and treatable ocular anomalies were identified. Higher OMENS-Plus classification orbit and soft tissue scores and Pruzansky–Kaban classification mandible scores were associated with an increased risk of ocular anomalies. Based on these results and the clinical implications ocular anomalies may have, we underline the importance of targeted ophthalmological screening in CFM. Healthcare professionals should be aware of the possibility of ocular anomalies in these patients, especially during the critical period for visual development.

Keywords: Goldenhar syndrome; craniofacial microsomia; oculo-auriculo-vertebral syndrome; oculoauriculovertebral dysplasia; hemifacial microsomia; eye; ophthalmology; strabismus; refractive errors; eyelid.

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Introduction

Craniofacial microsomia (CFM) is a congenital disorder affecting structures derived from the first and second pharyngeal arches. It is characterized by a diverse spectrum of anomalies, including underdevelopment of the mandible, orbit, ear, facial nerve, and soft tissues. The incidence ranges from one in 3000 to one in 26,000 live births, making it the second most common congenital anomaly of the head and neck.[1–5]

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The aetiology of CFM is unknown, but several theories exist, of which the originally proposed theory of haemorrhage of the stapedial artery during embryonic development is probably best known.[3,6] More recently, a disruption in the migration, proliferation, and differentiation of cranial neural crest cells to the branchial arches during embryonic development was proposed as playing a key role in the development of the malformations seen in CFM.[7,8]

The phenotype varies greatly between individuals, as different facial structures may be affected with varying severity. However, asymmetric underdevelopment of the mandible is considered to be one of the hallmark features of CFM.[9] The severity of the mandibular deformity can be assessed using the Pruzansky–Kaban classification.[10,11] This classification is based on radiographic imaging of the mandible. A score of 0 indicates a normal mandible, and a higher score indicates a more severely deformed mandible, with a score of 3 being the maximum.

The severity of hypoplasia of the affected facial structures in CFM can be classified using the OMENS-Plus classification.[12,13] Each letter of the acronym constitutes one of the five major craniofacial manifestations of CFM: Orbital distortion, Mandibular hypoplasia, Ear anomaly, facial Nerve involvement, and Soft tissue deficiency. Birgfeld et al. created the Phenotypic Assessment Tool for CFM (PAT-CFM), which is based on the OMENS-Plus and Pruzansky–Kaban classifications.[1] In the PAT-CFM, extra criteria are added for the assessment of specific facial anomalies, including ocular and adnexal anomalies, such as eyelid coloboma, epibulbar dermoid, and esotropia or exotropia.

Ocular and adnexal anomalies, both structural and functional, are frequently observed in patients with CFM.[14] Structural ocular anomalies range from lipodermoids to anophthalmia.[15–18] Functional ocular anomalies range from visual impairment to Duane syndrome.[16,19–21] Furthermore, corneal hypoesthesia and anomalies of the lacrimal apparatus are also described in patients with CFM, which can lead to corneal scarring and decreased visual acuity.[22–24]

Despite previous research on ocular anomalies in CFM, many aspects are still unclear or unknown. Incidences of the associated ocular anomalies are highly variable throughout the literature and remain unknown for many ocular and adnexal anomalies in patients with CFM.[14] This is likely due to the relatively small numbers of patients in previous research. Furthermore, the effect of ocular and adnexal anomalies on visual acuity is mostly unknown for CFM patients. Little is known about the relationship between ocular and adnexal anomalies and craniofacial and extracraniofacial anomalies in patients with CFM.

The aim of this study was to describe and categorize the types of ocular and adnexal anomalies diagnosed in patients with CFM and to determine their respective prevalence rates. Furthermore, an investigation of the association between the Pruzansky–Kaban and OMENS-Plus classifications and the presence of ocular anomalies was performed, in order to determine whether these classifications could be used to identify patients most at risk of ocular and adnexal anomalies.

Methods

This retrospective cohort study was conducted at four craniofacial centres: Erasmus Medical Center in Rotterdam, the Netherlands; Great Ormond Street Hospital in London, UK; the Boston Children's Hospital in Boston, USA; the Hospital for Sick Children in Toronto, Canada. The hospital databases were searched for patients with a diagnosis of CFM. This study was approved by the institutional review boards in Rotterdam (MEC-2013-575), London (14 DS25), Boston (X05-08-058), and Toronto (1000053298).

The following data were extracted from the electronic patient files and paper charts: patient demographics, i.e. sex and date of birth, the side of the face that was affected by CFM, the severity of the deformity, and the presence of ocular and adnexal anomalies. The charts of patients diagnosed with isolated microtia were screened for any additional findings that could indicate CFM. Patients with isolated microtia without any other manifestations of CFM were excluded.

As CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic X-rays and/or computed tomography scans of the head and neck, were included for analysis. If both clinical photographs and radiographic images were not available, the patient was excluded from further analysis.

The severity of the deformity of the affected facial structures was determined using the PAT-CFM, developed by Birgfeld et al.[1] All patients were assessed using either the Pruzansky–Kaban classification, the OMENS-Plus classification, or both.

Ocular anomalies

Ocular and adnexal anomalies were categorized into four different categories based on the classification for ocular anomalies in CFM as proposed previously by our research group[14]. Type I ocular anomalies were defined as anatomical ocular or adnexal anomalies that in general do not tend to impair vision. Type II ocular anomalies were defined as anatomical ocular or adnexal anomalies that impair, or are likely to impair vision. Motility disorders of the eye or adnexa were defined as type III ocular anomalies. Refractive errors were separately categorized as type IV ocular anomalies. There is no ranked order indicating a more or a less severe anomaly in these categories.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the incidence of ophthalmological anomalies. Equality of groups was tested using the Pearson χ^2 test for independence. Univariate binary logistic regression was used to assess the association between the presence of ocular anomalies and the OMENS-Plus classification. For the mandible scores, the Pruzansky–Kaban classification was used instead of the OMENS-Plus mandible score. As there were no normal mandibles (M0) in the study cohort based on the Pruzansky–Kaban classification, M1 mandibles were used as the reference indicator variable for univariate binary logistic regression analysis. Consequently, it was not possible to calculate odds ratios (OR) for the risk of ocular anomalies in M1 mandibles. Since no comparable research investigating the association between the OMENS-Plus or Pruzansky–Kaban classification and ocular anomalies was available, it was not possible to perform a power analysis. A P-value < 0.05 was considered to be statistically significant.

Results

A total of 881 CFM patients were included in the analysis; 470 (53.3%) were male and 411 (46.7%) were female. The side affected by CFM was reported in all 881 patients: 330 (37.5%) left side, 434 (49.3%) right side, and 117 (13.3%) bilateral.

The Pruzansky–Kaban classification was determined in 671 patients (76.2%). The OMENS-Plus classification was

Table 1. Patient demographics.

	Patients without ocular anomalies		Patients with ocular anomalies		Total	
Total	582	(66.1%)	299	(33.9%)	881	(100%)
Sex						
Male	322	(55.3%)	148	(49.5%)	470	(53.3%)
Female	260	(44.7%)	151	(50.5%)	411	(46.7%)
Laterality						
Unilateral	525	(90.0%)	239	(79.9%)	764	(86.6%)
Bilateral	57	(10.0%)	60	(20.1%)	117	(13.4%)
Affected side (UCFM)[a]						
Right	305	(58.1%)	129	(54.0%)	434	(56.8%)
Left	220	(41.9%)	110	(46.0%)	330	(43.2%)
Orbit[b]						
0	319	(54.8%)	91	(30.4%)	410	(46.5%)
1	87	(14.9%)	42	(14.0%)	129	(14.6%)
2	66	(11.3%)	37	(12.4%)	103	(11.7%)
3	51	(8.8%)	43	(14.4%)	94	(10.7%)
4	8	(1.4%)	30	(10.0%)	38	(4.3%)
Unknown	51	(8.8%)	56	(18.7%)	107	(12.1%)
Mandible[c]						
0	11	(1.9%)	4	(1.3%)	15	(1.7%)
1	187	(32.1%)	66	(22.1%)	253	(28.7%)
2A	153	(26.3%)	69	(23.1%)	222	(25.2%)
2B	122	(21.0%)	73	(24.4%)	195	(22.1%)
3	86	(14.8%)	75	(25.1%)	161	(18.3%)
Unknown[d]	23	(4.0%)	12	(4.0%)	35	(4.0%)
Ear[b]						
0	70	(12.0%)	44	(14.7%)	114	(12.9%)
1	66	(11.3%)	45	(15.1%)	111	(12.6%)
2	62	(10.7%)	33	(11.0%)	95	(10.8%)
3	303	(52.1%)	104	(34.8%)	407	(46.2%)
4	11	(1.9%)	11	(3.7%)	22	(2.5%)
Unknown	70	(12.0%)	62	(20.7%)	132	(15.0%)
Nerve[b]						
0	149	(25.6%)	77	(25.8%)	226	(25.7%)
1	34	(5.8%)	12	(4.0%)	46	(5.2%)
2	42	(7.2%)	24	(8.0%)	66	(7.5%)
3	25	(4.3%)	10	(3.3%)	35	(4.0%)
4	13	(2.2%)	7	(2.3%)	20	(2.3%)
Unknown	319	(54.8%)	169	(56.5%)	488	(55.4%)
Soft tissue[b]						
0	96	(16.5%)	24	(8.0%)	120	(13.6%)
1	228	(39.2%)	97	(32.4%)	325	(36.9%)
2	153	(26.3%)	90	(30.1%)	243	(27.6%)
3	40	(6.9%)	30	(10.0%)	70	(7.9%)
Unknown	65	(11.2%)	58	(19.4%)	123	(14.0%)

UCFM, unilateral craniofacial microsomia.
[a] In unilateral cases of craniofacial microsomia.
[b] Orbit, ear, nerve, and soft tissue score based on the OMENS-Plus classification.
[c] Mandible score based on the Pruzansky–Kaban classification.
[d] In five patients, the Pruzansky–Kaban classification could not be assessed due to surgical correction of the mandible.

determined in 791 patients (89.8%). At least one of the two classifications was assessed for every patient. Table 1 provides a detailed overview of patient characteristics and the OMENS-Plus classification for patients with and without ocular anomalies.

Ocular anomalies of any type were reported in 299 patients (33.9%); 151 (50.5%) were male and 148 (49.5%) were female. Unilateral ocular anomalies were present in 134 patients, of which the left eye was affected in 66 patients (49.3%) and the right eye in 68 patients (50.7%). Bilateral ocular anomalies were present in 128 patients. In 37 patients, the side affected by the ocular anomalies was unknown or not applicable. In patients with ocular anomalies, there was a significant association between the side of the face affected by CFM and the side of the affected eye (Pearson χ^2 (df = 4, $N = 261$) = 45.97, $P < 0.001$; Table 2). The mean number of ocular anomalies of any type per affected patient was 3.41 (standard deviation (SD) ± 2.69).

The prevalence of ocular anomalies did not differ between male and female patients (Pearson χ^2 (df = 1, $N = 881$) = 2.696, $P = 0.101$). Bilaterally affected patients had a significantly increased risk of ocular anomalies compared to unilaterally affected patients (OR 2.27, 95% confidence interval (CI) 1.54–3.36; Pearson χ^2 (df = 1, $N = 881$) = 17.38, $P < 0.001$).

Table 2. Relationship between laterality of CFM and side of ocular anomalies.

	Left eye		Right eye		Both eyes		Side unknown	
Unilateral CFM								
Left side affected	42	(38.2%)	10	(9.1%)	41	(37.3%)	17	(15.5%)
Right side affected	12	(9.3%)	47	(36.4%)	54	(41.9%)	16	(12.4%)
Bilateral CFM	12	(20.0%)	11	(18.3%)	33	(55.0%)	4	(6.7%)

CFM, craniofacial microsomia.

In total, 267 of 881 patients (30.3%) were examined by an ophthalmologist at some point during the course of follow-up. Of the 299 patients with ocular anomalies, 220 (73.6%) were examined by an ophthalmologist.

Type I ocular anomalies

Type I ocular anomalies were observed in 196 of 881 patients (22.2%) (Table 3). The left eye was affected in 44 patients, the right eye in 51 patients, and 48 patients were affected bilaterally. The affected side was unknown or not applicable in 53 patients. The mean number of type I ocular anomalies in affected patients was 1.38 (SD ± 0.72).

Type II ocular anomalies

Type II ocular anomalies were observed in 168 patients (19.0%) (Table 4). The left eye was affected in 64 patients, the right eye in 63 patients, and 38 patients were affected bilaterally. The affected side was unknown in three patients. The mean number of type II ocular anomalies in affected patients was 1.75 (SD ± 1.35).

Type III ocular anomalies

Type III ocular anomalies were seen in 162 patients (18.4%) (Table 5). Unilateral anomalies were seen in 102 patients, with 47 patients affected on the left side and 55 patients affected on the right side. Forty-eight patients were affected bilaterally. The side of the ocular anomalies was unknown in 12 patients. The mean number of type III ocular anomalies in affected patients was 1.53 (SD ± 0.81).

Type IV ocular anomalies

Type IV ocular anomalies were seen in 128 patients (14.5%) (Table 6). The left eye was affected in 40 patients, the right eye in 26 patients, and 48 patients were affected bilaterally. The mean number of type IV ocular anomalies in affected patients was 1.77 (SD ± 0.84).

Association between OMENS-Plus classification and ocular anomalies

Increased orbit scores of the OMENS-Plus classification (i.e. O1–O4) were significantly associated with an increased risk of ocular anomalies (Table 7), as were increased mandible scores (i.e. M2b and M3, based on the Pruzansky–Kaban classification) and soft tissue scores (i.e. S1–S3). Involvement of the facial nerve (i.e. N1–N4) was not associated with an increase or decrease in the risk of ocular anomalies. A severely malformed ear (i.e. E3) was associated with a significantly decreased risk of ocular anomalies (Table 7).

Discussion

The aim of this study was first of all to describe and categorize the different ocular and adnexal anomalies diagnosed in patients with CFM and to determine their respective prevalence. A total of 881 patients were included, of whom 299 (33.9%) were diagnosed with at least one ocular anomaly. Ocular and adnexal anomalies were categorized into four categories. Type I ocular anomalies were present in 22.2% of patients, type II ocular anomalies in 19.0%, type III ocular anomalies in 18.4%, and type IV ocular anomalies in 14.5%.

The results of this study are mostly similar to the results of previous research

Table 3. Type I ocular anomalies.

	Total		Left eye		Right eye		Both eyes		Unknown	
Lipodermoid	36	(4.1%)	18	(2.0%)	14	(1.6%)	4	(0.5%)		
Caruncle anomalies	10	(1.1%)			5	(0.6%)	5	(0.6%)		
Ectopic caruncle	7	(0.8%)			5	(0.6%)	2	(0.2%)		
Absent or hypoplastic caruncle	2	(0.2%)			1	(0.1%)	1	(0.1%)		
Bilobed medial caruncle	3	(0.3%)	1	(0.1%)	1	(0.1%)	1	(0.1%)		
Eyelid anomalies	54	(6.1%)	21	(2.4%)	25	(2.8%)	3	(0.3%)	5	(0.6%)
Symblepharon	4	(0.5%)	2	(0.2%)	2	(0.2%)				
Eyelid coloboma	42	(4.8%)	18	(2.0%)	19	(2.2%)	2	(0.2%)	3	(0.3%)
Eyelid entropion	13	(1.5%)	3	(0.3%)	8	(0.9%)			2	(0.2%)
Eyelid ectropion	3	(0.3%)	1	(0.1%)	2	(0.2%)				
Anomalous vessels fundus	8	(0.9%)	1	(0.1%)	5	(0.6%)	2	(0.2%)		
Hypopigmentation fundus	2	(0.2%)			1	(0.1%)	1	(0.1%)		
Nasolacrimal duct obstruction	20	(2.3%)	7	(0.8%)	9	(1.0%)	3	(0.3%)	1	(0.1%)
Iris coloboma	16	(1.8%)	6	(0.7%)	8	(0.9%)	2	(0.2%)		
Decreased sensation eye	11	(1.2%)	3	(0.3%)	6	(0.7%)	2	(0.2%)		
Lacrimal organ dysfunction	6	(0.7%)	1	(0.1%)	2	(0.2%)	1	(0.1%)	2	(0.2%)
Other	105	(11.9%)	12	(1.4%)	10	(1.1%)	19	(2.2%)	64	(7.3%)
Heterochromia	2	(0.2%)								
Congenital anomalous vessels conjunctiva	1	(0.1%)	1	(0.1%)						
Hypertelorism	6	(0.7%)								
Eye shape anomaly	13	(1.5%)								
Hypertropia	11	(1.2%)	4	(0.5%)	7	(0.8%)				
Hypotropia	8	(0.9%)	5	(0.6%)	3	(0.3%)				
Dystopia	71	(8.1%)								
Enophthalmos	3	(0.3%)	1	(0.1%)	2	(0.2%)				
Exophthalmos	4	(0.5%)	2	(0.2%)	2	(0.2%)				

Table 4. Type II ocular anomalies.

	Total		Left eye		Right eye		Both eyes		Unknown	
Epibulbar dermoid	95	(10.8%)	33	(3.7%)	39	(4.4%)	20	(2.3%)	3	(0.3%)
Microphthalmia	53	(6.0%)	25	(2.8%)	25	(2.8%)	3	(0.3%)		
Anophthalmia	7	(0.8%)	3	(0.3%)	4	(0.5%)				
Corneal anomalies	34	(3.9%)	16	(1.8%)	16	(1.8%)	2	(0.2%)		
Corneal damage	34	(3.9%)	16	(1.8%)	16	(1.8%)	2	(0.2%)		
Sclerocornea	2	(0.2%)	1	(0.1%)	1	(0.1%)				
Megalocornea	1	(0.1%)			1	(0.1%)				
Microcornea	2	(0.2%)	2	(0.2%)						
Congenital anomalous vessels	2	(0.2%)	1	(0.1%)			1	(0.1%)		
Lens or iris anomalies	10	(1.1%)	5	(0.6%)	3	(0.3%)			2	(0.2%)
Persistent tunica vasculosa lentis	3	(0.3%)	2	(0.2%)					1	(0.1%)
Persistent pupillary membrane	6	(0.7%)	5	(0.5%)	1	(0.1%)				
Congenital cataract	1	(0.1%)			1	(0.1%)				
Non-congenital cataract	2	(0.2%)	1	(0.1%)	1	(0.1%)				
Fundus anomalies	24	(2.7%)	6	(0.7%)	11	(1.2%)	7	(0.8%)		
Choroid retinal anomalies	24	(2.7%)	6	(0.7%)	11	(1.2%)	7	(0.8%)		
Chorioretinal atrophy	1	(0.1%)			1	(0.1%)				
Chorioretinal scar	2	(0.2%)			2	(0.2%)				
Chorioretinal coloboma	11	(1.2%)	3	(0.3%)	6	(0.7%)	2	(0.2%)		
Retinal detachment	2	(0.2%)	2	(0.2%)						
Retinal dystrophy	1	(0.1%)			1	(0.1%)				
Retinal hypoplasia	3	(0.3%)	1	(0.1%)	1	(0.1%)	1	(0.1%)		
Optic nerve anomalies	22	(2.5%)	7	(0.8%)	11	(1.2%)	4	(0.5%)		
Optic nerve hypoplasia	13	(1.5%)	2	(0.2%)	8	(0.9%)	3	(0.3%)		
Tilted optic disc	2	(0.2%)			2	(0.2%)				
Optic nerve coloboma	5	(0.6%)	3	(0.3%)	1	(0.1%)	1	(0.1%)		
Increased cup disc ratio	1	(0.1%)			1	(0.1%)				
Glaucoma	4	(0.5%)	3	(0.3%)	1	(0.1%)				
Axenfeld–Rieger syndrome	1	(0.1%)			1	(0.1%)				

Table 5. Type III ocular anomalies.

	Total		Left eye		Right eye		Both eyes		Unknown	
Ptosis	19	(2.2%)	7	(0.8%)	9	(1.0%)	3	(0.3%)		
Lagophthalmos	36	(4.1%)	15	(1.7%)	18	(2.0%)	3	(0.3%)		
Cycloplegia	2	(0.2%)	1	(0.1%)	1	(0.1%)				
Movement disorder concerning the superior oblique muscle	16	(1.8%)	4	(0.5%)	8	(0.9%)	4	(0.5%)		
Excyclotorsion fundus	3	(0.3%)			1	(0.1%)	2	(0.2%)		
Incyclotorsion fundus	1	(0.1%)	1	(0.1%)						
Brown syndrome	6	(0.7%)	2	(0.2%)	4	(0.5%)				
Other eye motility disorders	128	(14.5%)	40	(4.5%)	42	(4.8%)	35	(4.0%)	11	(1.2%)
Nystagmus	18	(2.0%)	7	(0.8%)	2	(0.2%)	8	(0.9%)	1	(0.1%)
Strabismus	117	(13.3%)	36	(4.1%)	42	(4.8%)	28	(3.2%)	11	(1.2%)
Esotropia	42	(4.8%)	12	(1.4%)	17	(1.9%)	10	(1.1%)	3	(0.3%)
Exotropia	39	(4.4%)	13	(1.5%)	15	(1.7%)	7	(0.8%)	4	(0.5%)
Duane syndrome	34	(3.9%)	8	(0.9%)	13	(1.5%)	11	(1.2%)	2	(0.2%)
V-pattern eye motility	7	(0.8%)								
Eye movement disorder undefined	5	(0.6%)	1	(0.1%)	1	(0.1%)	2	(0.2%)	1	(0.1%)
Horner syndrome	1	(0.1%)							1	(0.1%)

Table 6. Type IV ocular anomalies.

	Total		Left eye		Right eye		Both eyes		Unknown	
Anisometropia	35	(4.0%)								
Astigmatism	49	(5.6%)	15	(1.7%)	9	(1.0%)	20	(2.3%)	5	(0.6%)
Myopia	22	(2.5%)	5	(0.6%)	6	(0.7%)	10	(1.1%)	1	(0.1%)
Hyperopia	56	(6.4%)	10	(1.1%)	11	(1.2%)	28	(3.2%)	7	(0.8%)
Amblyopia	65	(7.4%)	35	(4.0%)	28	(3.2%)			2	(0.2%)

regarding the prevalence of specific ocular anomalies.[14] However, the overall prevalence of ocular anomalies in this study is greater than the reported 17–24% in other relatively large patient cohorts[13,18,25,26]; nevertheless, it should be noted that the aim of these previous studies was not always to report the prevalence of ocular

Table 7. Univariate logistic regression analysis for the association between the OMENS-Plus classification and the presence of ocular anomalies.

		Ocular anomalies				
		Type I	Type II	Type III	Type IV	Any type
Orbit						
O1	OR	**1.783**	**2.382**	1.539	1.208	**1.692**
	95% CI	1.067–2.978	1.398–4.059	0.880–2.691	0.656–2.227	1.095–2.617
	P-value	0.027*	0.001*	0.131	0.544	0.018*
O2	OR	**2.274**	1.534	1.790	1.020	**1.965**
	95% CI	1.339–3.864	0.813–2.896	0.997–3.212	0.506–2.056	1.234–3.129
	P-value	0.002*	0.187	0.051	0.955	0.004*
O3	OR	**3.817**	**3.086**	**2.276**	1.751	**2.956**
	95% CI	2.292–6.357	1.754–5.428	1.282–4.042	0.938–3.267	1.851–4.719
	P-value	<0.001*	<0.001*	0.005*	0.078	<0.001*
O4	OR	**10.328**	**11.118**	**10.880**	**5.566**	**13.146**
	95% CI	5.070–21.041	5.432–22.755	5.332–22.203	2.701–11.471	5.825–29.667
	P-value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Mandible (Pruzansky–Kaban)						
M1	OR	NP	NP	NP	NP	NP
	95% CI					
	P-value					
M2a	OR	1.119	0.918	1.002	0.792	1.047
	95% CI	0.641–1.954	0.503–1.676	0.559–1.796	0.427–1.470	0.650–1.687
	P-value	0.692	0.781	0.994	0.460	0.849
M2b	OR	1.464	1.370	1.307	0.787	**1.615**
	95% CI	0.855–2.507	0.778–2.411	0.746–2.289	0.424–1.460	1.019–2.561
	P-value	0.164	0.276	0.349	0.447	0.041*
M3	OR	**2.311**	**2.130**	**1.779**	1.328	**2.240**
	95% CI	1.360–3.926	1.224–3.706	1.020–3.101	0.740–2.382	1.401–3.582
	P-value	0.002*	0.007*	0.042*	0.342	0.001*
Ear						
E1	OR	1.037	0.986	1.035	0.837	1.085
	95% CI	0.574–1.873	0.532–1.825	0.552–1.940	0.441–1.586	0.636–1.851
	P-value	0.904	0.986	0.915	0.585	0.766
E2	OR	0.700	**0.466**	0.615	0.685	0.847
	95% CI	0.364–1.345	0.221–0.980	0.299–1.264	0.343–1.371	0.481–1.492
	P-value	0.284	0.044*	0.186	0.285	0.565
E3	OR	**0.542**	**0.503**	**0.592**	**0.369**	**0.546**
	95% CI	0.331–0.887	0.300–0.844	0.351–0.999	0.214–0.637	0.352–0.846
	P-value	0.015*	0.009*	0.049*	<0.001*	0.007*
E4	OR	1.600	1.208	2.034	0.534	1.591
	95% CI	0.610–4.193	0.430–3.394	0.767–5.395	0.147–0.1949	0.636–3.980
	P-value	0.339	0.720	0.154	0.343	0.321
Nerve						
N1	OR	0.738	1.111	0.520	0.877	0.683
	95% CI	0.336–1.625	0.479–2.578	0.175–1.541	0.345–2.233	0.335–1.394
	P-value	0.451	0.806	0.238	0.784	0.295
N2	OR	0.745	1.295	1.469	1.575	1.106
	95% CI	0.378–1.466	0.641–2.616	0.736–2.934	0.785–3.159	0.624–1.959
	P-value	0.394	0.472	0.275	0.201	0.731
N3	OR	0.506	0.495	1.364	0.755	0.774
	95% CI	0.187–1.367	0.144–1.703	0.553–3.366	0.250–2.278	0.354–1.694
	P-value	0.179	0.264	0.500	0.617	0.522
N4	OR	1.012	0.586	1.364	1.462	1.042
	95% CI	0.352–2.910	0.130–2.638	0.431–4.323	0.460–4.646	0.399–2.719
	P-value	0.982	0.487	0.598	0.520	0.933
Soft tissue						
S1	OR	**1.966**	1.357	**2.426**	1.552	**1.702**
	95% CI	1.059–3.651	0.705–2.612	1.112–5.292	0.773–3.114	1.025–2.824
	P-value	0.032*	0.361	0.026*	0.217	0.040*
S2	OR	**2.650**	1.871	**3.905**	1.667	**2.353**
	95% CI	1.416–4.960	0.966–3.621	1.792–8.513	0.815–3.412	1.402–3.948
	P-value	0.002*	0.063	0.001*	0.162	0.001*
S3	OR	**2.821**	**4.028**	**5.600**	1.847	**3.000**
	95% CI	1.310–6.073	1.881–8.627	2.311–13.570	0.756–4.516	1.564–5.754
	P-value	0.008*	<0.001*	<0.001*	0.178	0.001*

OR, odds ratio; 95% CI, 95% confidence interval; NP, not possible to calculate the OR and corresponding 95% CI and *P*-value. Statistically significant findings are marked with an asterisk (*).

anomalies. Furthermore, these studies did not report whether the patients underwent screening for ocular anomalies by an ophthalmologist. It could therefore be that the prevalence of ocular anomalies was underreported in these previous studies.

Furthermore, we report a number of clinically significant ocular anomalies, whereby several treatable and preventable ocular anomalies that may cause visual impairment were identified.[27,28] First of all, anomalies that may cause corneal damage were reported, i.e. eyelid coloboma (prevalence of 4.8%), entropion (1.5%), decreased sensation of the eye (1.2%), and lagophthalmos (4.1%). Corneal damage, reported in 3.9% of patients, causes severe discomfort for patients and may cause visual impairment if not adequately treated in a timely manner.[29] Furthermore, epibulbar dermoids, one of the most often described ocular features of CFM (reported in 10.8% of patients), can lead to severe astigmatism, a type IV anomaly, which in turn may cause amblyopia.[30] Generally, epibulbar dermoids are better left untouched, but in selected cases timely surgical removal of the epibulbar dermoid can prevent amblyopia, thereby preserving visual acuity.[31,32] Finally, type IV anomalies (14.5%), which often require orthoptic examination to diagnose, require timely diagnosis and treatment during the sensitive period of visual development in order to prevent visual impairment.[33] It is therefore critical that patients at risk of these anomalies are diagnosed and treated in time, preferably before the age of 5 years, to prevent visual impairment.[32]

This study also investigated the association between the Pruzansky–Kaban and OMENS-Plus classifications and the risk of ocular anomalies. Increased orbit, mandible, and soft tissue scores were associated with an increased risk of ocular anomalies, and a severely malformed ear (E3) was associated with a decreased risk of ocular anomalies.

It appears that the Pruzansky–Kaban and OMENS-Plus classifications have not been used to identify patients at risk of ocular anomalies before. A comparison of the present study data with the data obtained in other studies was therefore not possible. However, some studies have investigated the association between the Pruzansky–Kaban or OMENS classification and the presence of extracraniofacial anomalies in CFM. Horgan et al. reported a higher risk of extracraniofacial anomalies with increasing cumulative OMENS scores.[34] Renkema et al. found that higher OMENS-Plus nerve and soft tissue scores and higher Pruzansky–Kaban classification scores were associated with an increased risk of extracraniofacial anomalies.[35]

It seems logical that patients with more severely hypoplastic facial structures are at increased risk of ocular anomalies. However, none of the proposed aetiologies of CFM fully explain the combination of anomalies observed in the clinical spectrum of CFM, or the relationships between these anomalies.[3,6,7,36] For example, haemorrhage of the stapedial artery and a disruption of Meckel's cartilage may explain hypoplasia of the facial skeleton, but inducing this haemorrhage in an animal study did not result in the typical ocular anomalies seen in CFM.[3] Furthermore, the theory does not provide an explanation for how extracraniofacial anomalies occur, and haemorrhage of the stapedial artery did not result in bilateral manifestations of CFM.[3,6] A disrupted migration of neural crest cells provides a better explanation for bilateral and extracraniofacial manifestations. It may also explain the relationship between craniofacial hypoplasia and ocular anomalies, since neural crest cells are involved in the embryonic development of both the facial skeleton and the eye.[37,38] However, no study so far has been able to create an animal model based on a disruption of migration of neural crest cells that embodies all of these manifestations of CFM.[3,6,8,36]

Moreover, based on these theories we cannot explain how a severely malformed ear would lower the risk of ocular anomalies. Rather, this finding supports the conclusion of earlier research that CFM embodies a spectrum of anomalies wherein overlapping clusters of anomalies exist, which can be explained by a combination of genetic, epigenetic, and non-genetic factors, rather than one unifying causative factor.[7,26,39] Further research is warranted to explore the aetiology of CFM and to better understand the relationships between the different manifestations.

This study is unique in that it describes ocular anomalies in the largest cohort of patients with CFM to date, thereby offering a detailed overview of the types and prevalence of ocular anomalies. Furthermore, this original study is novel in categorizing ocular anomalies using the classification proposed by our research group,[14] which offers a relatively concise separation of the anomalies and the impact they may have on the patient.

However, there are several limitations to this study. First of all, due to its retrospective nature and the absence of a screening protocol for ocular anomalies in the participating hospitals, only 30.3% of patients underwent a full ocular examination by an ophthalmologist and/or optometrist. It could be inferred that patients who do not have obvious anomalies at the time of diagnosis may not be sent for routine ophthalmological assessment. As such, several ocular anomalies were likely underreported, as some ocular anomalies can only be diagnosed using advanced ophthalmological diagnostic techniques. In comparison, Hertle et al. reported a 67% prevalence of ocular anomalies in 49 patients who all underwent ophthalmological examination, which is considerably higher than was found in the present study.[16] Furthermore, reporting of ocular anomalies in the patient files was not standardized or structured. It is therefore possible that ocular anomalies are not reported in patient files, causing underreporting of ocular anomalies.

In light of the results of this study, we recommend that healthcare professionals are highly attentive to the presence of ocular anomalies, especially during the sensitive period of visual development, i.e. birth to about 5 years of age (amblyopia may develop until about 8 years of age), as timely intervention significantly improves the visual prognosis.[32,40] Healthcare professionals should especially be aware of possible ocular anomalies in patients with a more severe craniofacial deformity and/or bilateral involvement. Furthermore, we emphasize the importance of ophthalmological screening for CFM patients, in accordance with recently published European guidelines on CFM.[32] The results of this study may aid in developing targeted screening guidelines.

Further clinical research should focus on the effect of different ocular anomalies on visual acuity and the effect of preventive measures or treatment strategies for these anomalies. A detailed screening protocol for ocular anomalies in CFM patients should be developed and validated to identify patients at risk of visual impairment. Finally, the effect of ophthalmological screening for patients with CFM should be evaluated in a prospective study.

In conclusion, this study reports a prevalence of ocular anomalies of 33.9% in patients with CFM. The types and respective prevalence of different ocular anomalies in a cohort of 881 CFM patients have been described. Ocular anomalies were separated into four subtypes, thereby providing a clinically relevant overview. Higher OMENS-Plus orbit and soft tissue scores and Pruzansky–Kaban classification mandible scores were associated with an increased risk of ocular anomalies.

Several preventable and/or treatable ocular anomalies that may cause visual impairment were identified. As these anomalies are relatively common and may have important clinical consequences, it is recommended that healthcare professionals involved in the care of these patients are highly aware of the possibility of ocular anomalies, especially during the sensitive period of visual development, and we highlight the importance of targeted ophthalmological screening in CFM.

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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

Ethical approval was given by the institutional review boards in Rotterdam, the Netherlands (MEC-2013-575); London, UK (14 DS25); Boston, USA (X05-08-058); and Toronto, Canada (1000053298).

Patient consent

Patient consent was not required.

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