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Systematic Review
Craniofacial Anomalies

Ocular and adnexal anomalies in craniofacial microsomia: a systematic review

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Abstract. Ocular anomalies may occur in craniofacial microsomia (CFM). The aim of this systematic review was to review the literature on ocular anomalies and their incidence, in order to estimate the need for ophthalmological screening in CFM patients. Online databases were searched, and data on the number of patients, type and incidence of ocular anomalies, and visual acuity were extracted. Four subgroups of ocular and adnexal anomalies were identified, to provide an overview of the different anomalies. Twenty-five papers analysing 1419 patients in total were included. Ocular anomalies were documented in 6.7–100% of patients. The most reported type I ocular anomalies were eyelid coloboma, lipodermoids, and orbital dystopia. The most reported type II ocular anomalies were epibulbar dermoid, microphthalmia, and anophthalmia. Ptosis and strabismus were the most reported type III anomalies, and irregular astigmatism was the most reported type IV ocular anomaly. Visual impairment in general was reported in 8–71.4% of patients, with severe visual impairment in 11.1–71.4% and amblyopia in 16.3%. This study provides a detailed overview of ocular anomalies in CFM and their prevalence. Furthermore, we propose a new classification to organize ocular anomalies into four clinically relevant subtypes. Finally, the high prevalence of ocular anomalies and visual impairment in this study suggests that CFM patients should undergo ophthalmological screening at least once during the sensitive period.

Key words: craniofacial microsomia; oculo-auriculo-vertebral syndrome; hemifacial microsomia; Goldenhar syndrome; ocular anomalies; adnexal anomalies; systematic review.

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Craniofacial microsomia (CFM) is a rare congenital disorder affecting structures derived from the first and second branchial arches. With an incidence of 1:3000 to 1:20,000 live-births, it is the second most common congenital craniofacial disorder after cleft lip and palate[1–5]. The disorder is characterized by underdevelopment of the orbit, mandible, ear, facial nerve, and soft tissues. Furthermore, several extracraniofacial malformations, i.e. cardiac, renal, vertebral, and central nervous system anomalies, are associated with CFM[6,7]. In addition to anatomical anomalies, functional anomalies, such as feeding difficulties and obstructive sleep apnoea, have also been associated with CFM[8–11].

CFM is known by several synonyms, including the first and second branchial arch syndrome, hemifacial microsomia, and lateral facial dysplasia. Goldenhar

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described CFM patients with ocular dermoids and extracraniofacial anomalies as a subtype of CFM, known as Goldenhar–Gorlin syndrome, Goldenhar syndrome (GS), or oculo-auriculo-vertebral spectrum (OAVS)[12–14]. However, Vento et al. refuted GS/OAVS as a subtype of CFM, as they found no association between these anomalies[15]. Tuin et al. concluded that use of the term GS is inconsequential, as not all GS patients meet the diagnostic criteria[16]. Also, Caron et al. recently concluded that there are no phenotypically distinct groups in the CFM spectrum[17]. In this paper we will therefore use CFM to refer to all earlier synonyms and GS/OAVS.

Several ocular and adnexal anomalies have been described in CFM. These anomalies include epibulbar dermoids, lipodermoids, eyelid coloboma, microphthalmia, anophthalmia, and anomalies of the lacrimal caruncle. Furthermore, visual impairment, strabismus, and Duane syndrome have been described in CFM.

The aim of this study was to document the different types and incidence rates of ocular anomalies in order to recognize and treat these as early as possible and thereby prevent or limit the lasting consequences of the anomalies.

Methods

Search strategy

A systematic search of the literature was conducted to identify papers on CFM (or its synonyms) and ocular or adnexal anomalies. The search was conducted in the PubMed, Embase, MEDLINE, Ovid, Cochrane, Web of Science, and Google Scholar databases. The databases were searched from inception until March 2016. The full search string used in the databases is included in Appendix A (**Supplementary Material**). For clarification, known synonyms of CFM that were used in the search are included in Appendix B (**Supplementary Material**). In addition, a manual search was performed to identify secondary sources in the references of the articles initially identified. No date limit was applied, but the results were limited to human subjects and papers written in English. Case reports, conference abstracts, letters, notes, and editorials were excluded.

Two investigators (W.R. and C.J.J.M.C) independently selected the studies. Titles and abstracts were screened for relevance and selected based on the inclusion and exclusion criteria. Inclusion criteria were (1) CFM or one of its synonyms, and (2) ocular or adnexal anomalies. Only original studies were included. Articles for which the titles and abstracts were missing sufficient information to determine eligibility according to the inclusion and exclusion criteria underwent a full-text review.

Data extraction

Prior to data extraction, a table was established with the study characteristics to be assessed during the full text review. This included data on the type of study, number of patients included, number of affected patients, availability of vision tests, and number of ocular anomalies per patient. Specific ocular anomalies were noted separately in this table. All studies were graded on quality of evidence using the Oxford Centre for Evidence-Based Medicine criteria.

Classification of ocular anomalies

Ocular anomalies were categorized into four different categories. 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.

Results

A total of 4900 papers were identified in the initial search, of which 2754 were screened after the duplicates had been removed. Of these, 2713 records were excluded after screening the title and abstract for relevance. Forty-one full-text records were screened for eligibility. In total, 25 records were included for qualitative analysis. A PRISMA diagram of the record selection process is presented in Fig. 1.

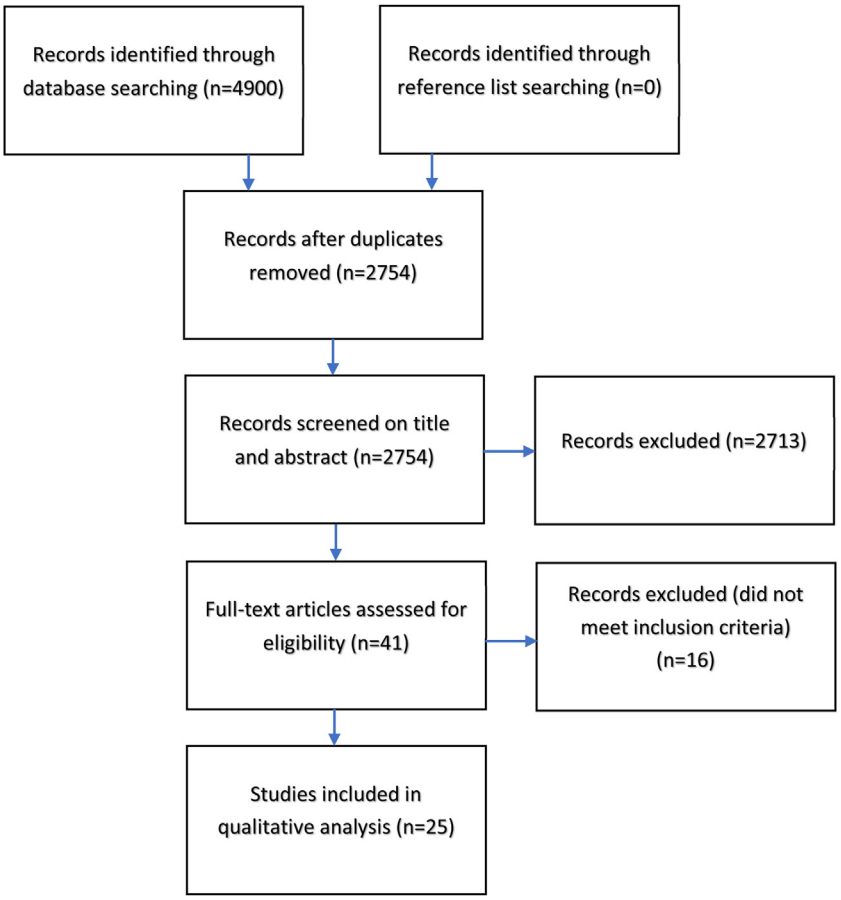

Fig. 1. PRISMA diagram of the record selection process.

Study characteristics

Of the 25 records included, 14 were retrospective studies[15,16,18–29], one was a prospective study[30], and 10 were case series[31–40]. The prospective study also had a retrospective component, in which patient charts were reviewed for additional information. Patients with isolated microtia were included in four studies; where possible, these patients were excluded from further analysis. A total of 1432 patients were analysed in this literature review, but it should be noted that 13 patients were analysed twice, once by Baum and Feingold[31] and once by Feingold and Baum[34], bringing the total to 1419 patients in 25 records. The number of patients per record varied from 6 to 294 patients. The characteristics of the included studies are reported in Table 1.

Documented type I ocular anomalies

Type I ocular anomalies were described in 22 records[15,16,18–28,30–34,36,37,39,40]. The most described anomaly was eyelid coloboma in 13 records, with incidences ranging between 3.9% and 40%[18,19,21,23,24,26,27,31,32,34,37,39,40]. Orbital dystopia was described in seven records, with incidences ranging between 3.9% and 43%[15,16,19,20,25,26,32]. Lipodermoids were described in six records, with incidences ranging from 4.1% to 75%[22,26,30,31,33,34]. Anomalies of the lacrimal organ, e.g. dacryostenosis, tear duct hypoplasia, and/or tear duct obstruction were described in seven records, with incidences ranging from 4.8% to 14.3%[21,22,24,26,31,33,40]. An iris coloboma was described in five records, in 1.5–30% of patients[18,21,26,31,36].

Three records described dystopia canthorum as a separate entity, with incidences ranging from 3.9% to 45.8%[19,22,28]. Telecanthus was described in two records, with an incidence of 2–4.8%[22,33]. Epicanthus and antimongoloid slanting of the eyelids were both described in three records, with incidences ranging between 5.4% and 5.9% and between 14.3% and 15.4%, respectively[18,19,26,31,36]. Three records described caruncle anomalies (incidence 1.8–14.3%)[24,31,36], one described eyelid tags (7.7%) and eyebrow coloboma (7.7%)[31], and one record described eyelid retraction in 2% of patients[22].

Tortuous retinal vessels (1.8–14.3%) were described in three records[22,24,36]. Mansour et al. also described fundus hypopigmentation in one of 57 patients[24]. Baum and Feingold separately described canthus coloboma in 23.1% of patients[31], and Hertle et al. described entropion in 4.1% of patients[22]. An overview of the type I ocular anomalies is presented in Table 2.

Documented type II ocular anomalies

Type II ocular anomalies were described in 21 records[15,16,18–21,23–27,30–37,39,40]. Epibulbar dermoids were the most often described, reported in 15 records, with incidences ranging from 6.7% to 100%[15,16,18,19,21,24,26,30–34,37,39,40]. Tasse et al. described a 20.4% incidence of ocular dermoids, not differentiating between epibulbar dermoids and lipodermoids[27]. Microphthalmia was described in 14 records, with incidences ranging from 1.8% to 57.1%[15,16,18–20,24–26,30,31,33,36,37,40]. Anophthalmia was described in six records, with incidences ranging between 1.5% and 42.9%[18,21,23,27,36,37]. Cryptophthalmos was described by Baum and Feingold in 7.7% of patients[31].

Exposure keratitis and cornea ulcer were described in 30% and 7.7%, respectively[31,39]. Baum and Feingold also described a microcornea in 15.4% of patients[31]. An opacity of the lens was described in two records, but only Ewart-Toland et al. reported the incidence, at 4.8%[26,33]. Barisic et al. described a complete absence of the lens in one of the 259 patients included[18].

Four records described optic nerve anomalies in 4.8–14.3% of patients, with Ewart-Toland et al. specifically describing optic nerve hypoplasia in 4.8% of patients[26,33,35,36]. Two records reported a fundus coloboma in 1.8% and 7.7% of patients, respectively[24,31]. An overview of the type II ocular anomalies is presented in Table 3.

Documented type III ocular anomalies

Type III ocular anomalies were described in 13 records[21–24,26–28,31,34–36,39,40]. Ptosis was most frequently described (in six records), with an incidence of 8.3–14.3%[22,24,26,28,36,39]. Furthermore, Manara et al. and Margolis et al. described anomalies of the abducens nerve in 27.6% and 28.6% of patients, respectively[35,36]. Manara et al. also described anomalies of the oculomotor, trigeminal, facial, and vestibulo-cochlear nerve in 3.4%, 37.9%, 37.9%, and 27.6%, respectively[35].

Anomalies concerning the motility of the eye were frequently described, but not always specified. Four records described extraocular muscle anomalies (not specified) in 19–38.5% of patients[24,31,34,39].

Strabismus (cause not specified) was described in five records, with an incidence of 7.7–22%[21,22,26,27,40]. Five records specified the type of strabismus: Duane syndrome (1.8–15.4%), esotropia (4.1–15.4%), and exotropia (5.3–7.7%) were reported[22,24,26,31,36]. Hertle et al. and Jacobsson and Granström also described abducens nerve palsy separately in 4.1% and 26.9% of patients, respectively[22,23]. Furthermore, Hertle et al. described superior oblique muscle palsy, strabismus sursoadductorius, and monofixation syndrome as specific eye motility disorders[22]. Finally, Baum and Feingold described hypertropia in one out of 13 patients[31]. An overview of the type III ocular anomalies is presented in Table 4.

Documented type IV ocular anomalies

Type IV ocular anomalies were described in three records[22,31,33]. Hertle et al. described refractive errors in 27% of patients, with irregular astigmatism being the most frequently described anomaly in 18.4–76.9% of patients[22,31]. Anisometropia was described in 16.3%[22]. Hyperopia was described in 4.1%[22]. Finally, myopia was described in 4.1–4.8% of patients[22,33]. An overview of the type IV ocular anomalies is presented in Table 5.

Documented visual acuity

Visual acuity was described in three papers[22,30,36]. Visual impairment was described in 8–71.4% of patients, of whom 11.1–71.4% were described as having severe visual impairment[30,36]. The definition of severe visual impairment was not provided in these papers. Strömland et al. reported five of 16 patients with visual acuity $\leq$0.3 LogMAR and two of 16 as blind[30]. Amblyopia was described in 16.3% by Hertle et al., indicating a unilateral visual acuity worse than 20/40[22]. Margolis et al. described visual acuity testing in two patients, one patient with a unilateral visual acuity of 20/200 and one with a unilateral visual acuity of finger counting at three feet[36].

Discussion

The aim of this systematic review was to describe the incidence and types of ocular anomalies in CFM. This systematic review is novel, particularly in regard to the attempted classification of the different ocular and adnexal anomalies. It should be noted that this is not an

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Table 1. Study characteristics.

Year	Author	CEBM level of evidence	Number of patients included	Methodology	Inclusion criteria of the study	% ocular anomalies
2014	Barisic et al.[18]	3	259	Retrospective study	Microtia or ear anomaly and one of the following anomalies: HFM, epibulbar dermoid, vertebral malformation	24.3%
1973	Baum and Feingold[31]	4	13	Case series	Unknown/GS	100%
2015	Beleza-Meireles et al.[19]	3	51	Retrospective study	Facial asymmetry and microtia or ear malformations	29%
1974	Converse et al.[32]	4	15	Case series	Bilateral CFM	6.7%
1993	Cousley[20]	3	50	Retrospective study	HFM	49% of 53 affected sides (3 patients were affected bilaterally)
2015	da Silva et al.[21]	3	20	Retrospective study	Inclusion criteria for CFM by Strömland et al. (OAVS phenotype with anomalies in at least 2 of the following: orocraniofacial, ocular, auricular, and/or vertebral)	60%
2000	Ewart-Toland et al.[33]	4	14	Case series	OAVS patients born of diabetic mothers	57%
1978	Feingold and Baum[34]	4	16[a]	Case series	Eye anomaly (lipodermoid/epibulbar dermoid/upper eyelid coloboma) and two of the following: ear/mandible/vertebral anomaly	100%
1992	Hertle et al.[22]	3	49	Retrospective study	HFM/CFM with complete ocular examination, GS was excluded	67%
1997	Jacobsson and Granström[23]	3	26	Retrospective study	Unilateral HFM with ear anomaly and malar bone hypoplasia and/or maxillary and/or mandibular micrognathia	At least 27%
2015	Manara et al.[35]	4	29	Case series	OAVS patients with neuro-imaging studies	Not possible to calculate
1985	Mansour et al.[24]	3	57	Retrospective study	Facio-auriculo-vertebral sequence	51%
1984	Margolis et al.[36]	4	7	Case series	GS	At least 57%
2010	Martelli et al.[37]	4	6	Case series	GS diagnosed with criteria by Strömland et al.	66.7%
2002	Nijhawan et al.[38]	4	7	Case series	GS with caruncle anomalies	100%
2003	Poon et al.[25]	3	65	Retrospective study	HFM/OAVD/facio-auricular-vertebral dysplasia/GS	23% (anomaly in OMENS 'O')
2001	Rahbar et al.[29]	3	40	Retrospective study	HFM with temporal bone CT scan	12.5% (anomaly in OMENS 'O')
1982	Rao et al.[39]	4	10	Case series	GS	100%
1987	Rollnick et al.[26]	3	294	Retrospective study	Microtia	20%
2010	Rosa et al.[40]	4	17	Case series	OAVS (at least two of the following: orocraniofacial, ocular, auricular, vertebral) and radiographic imaging (CT/MRI) of CNS and normal karyotype	At least 24%
2007	Strömland et al.[30]	3	18	Retro- and prospective study	GS/OAVS/HFM (at least two of the following: orocraniofacial, ocular, auricular, vertebral)	72%
2005	Tasse et al.[27]	3	53	Retrospective study	OAVS (minimal diagnostic criteria, isolated microtia or HFM with mild ear malformations)	At least 31%
2015	Tuin et al.[16]	3	138	Retrospective study	CFM or GS	At least 17%
1991	Vento et al.[15]	3	154	Retrospective study	HFM and/or microtia	At least 21%
1979	Whitaker et al.[28]	3	24	Retrospective study	HFM patients who underwent craniofacial surgery	At least 46%

CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia; CNS, central nervous system; CT, computed tomography; GS, Goldenhar syndrome; HFM, hemifacial microsomia; MRI, magnetic resonance imaging; OAVD, oculo-auriculo-vertebral dysplasia; OAVS, oculo-auriculo-vertebral syndrome.

[a] Thirteen patients were also analysed by Baum and Feingold[31].

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Table 2. Percentage of patients with type I ocular anomalies per record.

Author	Included patients	Lipodermoids	Iris coloboma	Telecanthus	Epicanthus	Antimongoloid slant	Caruncle anomalies	Eyelid coloboma	Orbital dystopia	Dystopia canthorum	Dacryostenosis	Tear duct hypoplasia/ obstruction	Tortuous retinal vessels
Barisic et al.[18]	259		1.5		5.4			3.9					
Baum and Feingold[31]	13	61.5	15.4			15.4	7.7	30.8				15.4	
Beleza-Meireles et al.[19]	51				5.9			3.9	3.9	3.9			
Converse et al.[32]	15							6.7	6.7				
Cousley[20]	50								43				
da Silva et al.[21]	20		30					5			5		
Ewart-Toland et al.[33]	14	9.5		4.8								4.8	
Feingold and Baum[34]	16	75						25					
Hertle et al.[22]	49	4.1		2						8.2	14.3		2
Jacobsson and Granström[23]	26							11.5					
Mansour et al.[24]	57						1.8	11			3.5	3.5	1.8
Margolis et al.[36]	7		28.6			14.3	14.3						14.3
Martelli et al.[37]	6							16.7					
Poon et al.[25]	65								11				
Rao et al.[39]	10							40					
Rollnick et al.[26]	294	*	*		*	*		*	*			*	
Rosa et al.[40]	17							11.8			5.9		
Strömland et al.[30]	18	61.1											
Tasse et al.[27]	53							7.7					
Tuin et al.[16]	138								11.2				
Vento et al.[15]	154								15				
Whitaker et al.[28]	24									45.8			

Please note that not all type I ocular anomalies are presented in this table; incidences of lacrimal apparatus anomalies, eyelid tags, eyebrow coloboma, and eyelid retraction are mentioned in the text.
* Not possible to calculate percentage.

empirical classification, but that the classification is based on multiple focus group discussions with experts in the field. There is insufficient data supporting the claims that certain anatomical anomalies do not cause visual impairment, as in type I ocular anomalies, and that certain anatomical anomalies do cause visual impairment, as in type II ocular anomalies. For example, based on the anatomical location and the extent of the anomaly, a lipodermoid could theoretically impair vision. However, in our experience this rarely occurs. Further research is needed to investigate the relationships between anatomical anomalies and visual impairment.

Most records described type I and type II ocular anomalies, specifically epibulbar dermoids, eyelid colobomas, and microphthalmia[15,16,18–21,23–27,30–34,36,37,39,40]. Photographs of these anomalies are presented in Figs 2–4, respectively. It is worth noting that Baum and Feingold described a canthus coloboma[31], which is an unusual finding in CFM, as colobomas in CFM usually involve the upper eyelid and not the canthus region. Many anomalies were only described in a few papers and in general showed relatively small incidence rates, indicating that these anomalies are likely easily overlooked.

The wide range of incidences of ocular anomalies, between 6.7% and 100%, can be attributed to the difference in patient selection, aim of the study, and methodology. For instance, in a study investigating GS, the incidence of ocular anomalies should be 100%, as an epibulbar dermoid is part of the definition of GS; this was the case in three studies[31,38,39]. However, as stated previously by Tuin et al., the definition of GS is seldom followed[16]. It is also important to note that a recent study found no phenotypically distinctive groups in the CFM spectrum, thereby indicating that there are no grounds to identify GS as a separate entity within the CFM spectrum[17]. Furthermore, the inclusion and exclusion criteria in the included papers varied substantially or were unknown, explaining the different incidences of ocular anomalies to some extent. It should be noted that only Hertle et al.[22] excluded patients without a known ophthalmological examination, as their aim was to document ocular anomalies in CFM. None of the other papers had the sole aim of describing ocular anomalies. It therefore seems likely that the incidence of ocular anomalies lies close to 67%, as described by Hertle et al.[22].

Furthermore, only seven papers described anomalies that could only

Table 3. Percentage of patients with type II ocular anomalies per record.

Author	Included patients	Microphthalmia	Anophthalmia	Epibulbar dermoid	Exposure keratitis/cornea ulcer	Opacity lens	Fundus coloboma	Optic nerve anomalies
Barisic et al.[18]	259	5.4	1.5	7.7				
Baum and Feingold[31]	13	7.7		69.2	7.7		7.7	
Beleza-Meireles et al.[19]	51	3.9		15.7				
Converse et al.[32]	15			6.7				
Cousley[20]	50	15						
da Silva et al.[21]	20		10	25				
Ewart-Toland et al.[33]	14	9.5		14.3		4.8		4.8
Feingold and Baum[34]	16			62.5				
Jacobsson and Granström[23]	26		3.8					
Manara et al.[35]	29							13.8
Mansour et al.[24]	57	1.8		32			1.8	
Margolis et al.[36]	7	57.1	42.9					14.3
Martelli et al.[37]	6	50	16.7	33.3				
Poon et al.[25]	65	12						
Rao et al.[39]	10			100	30			
Rollnick et al.[26]	294	*		*		*		*
Rosa et al.[40]	17	11.8		23.5				
Strömland et al.[30]	18	22.2		44.4				
Tasse et al.[27]	53		3.8					
Tuin et al.[16]	138	14.4		17				
Vento et al.[15]	154	4		20.8				

* Not possible to calculate percentage.

Table 4. Percentage of patients with type III ocular anomalies per record.

Author	Included patients	Ptosis	Extraocular muscle anomaly (undefined)	Strabismus (undefined)	Duane syndrome	Esotropia	Exotropia	Abducens nerve palsy	Abducens nerve anomaly	Nystagmus
Baum and Feingold[31]	13		38.5		15.4	15.4	7.7			
da Silva et al.[21]	20			15						
Feingold and Baum[34]	16		31.3							
Hertle et al.[22]	49	12.2		22	6.1	4.1	6.1	4.1		6.1
Jacobsson and Granström[23]	26							26.9		
Manara et al.[35]	29								27.6	
Mansour et al.[24]	57	12	19		1.8	10.5	5.3			
Margolis et al.[36]	7	14.3				14.3			28.6	
Rao et al.[39]	10	*	*							
Rollnick et al.[26]	294	*		*		*				*
Rosa et al.[40]	17			11.8						5.9
Tasse et al.[27]	53			7.7						
Whitaker et al.[28]	24	8.3								

* Not possible to calculate percentage.

Table 5. Percentage of patients with type IV ocular anomalies per record.

Author	Included patients	Refractive errors (undefined)	Irregular astigmatism	Anisometropia	Hyperopia	Myopia
Baum and Feingold[31]	13		76.9			
Ewart-Toland et al.[33]	14					4.8
Hertle et al.[22]	49	27	18.4	16.3	4.1	4.1

be seen while performing fundoscopy[22,24,26,31,33,35,36] and three papers described visual acuity[22,31,33]. This suggests that most papers did not include information about ophthalmological examinations, or that patients simply had not undergone an ophthalmological examination. In light of the data, specifically the large incidence of (severe) visual impairment and preventable causes of visual impairment, such as exposure keratitis in 7.7–30%, we strongly recommend that all CFM patients undergo a full ophthalmological and orthoptic examination at least once during the sensitive period. It is beyond the scope of this review to discuss the treatment options and timing of treatment for the ocular

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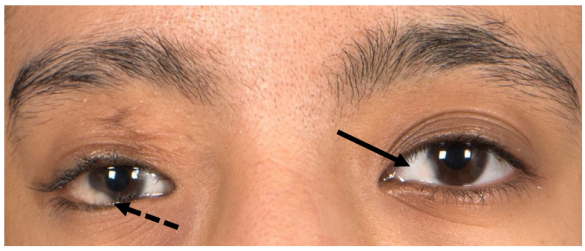

Fig. 2. Picture showing an epibulbar dermoid in both the right and left eye (arrows).

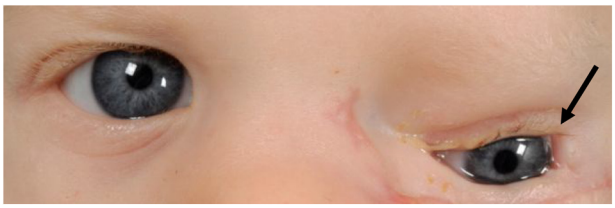

Fig. 3. Picture showing a normal right eye and anomalies of the left eye: there is an upper eyelid coloboma (arrow) and dystopia with inferior displacement of the left orbit.

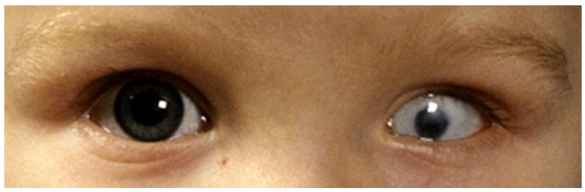

Fig. 4. Picture showing a normal right eye and a microphthalmic left eye.

anomalies described. Further research is needed to develop a specific screening protocol for CFM patients.

In conclusion, this article provides a detailed overview of the known ocular anomalies in CFM patients and their respective incidences. Ocular anomalies were present in 6.7–100% of patients. We propose a classification for ocular anomalies, identifying four different types of ocular anomalies, to offer a relatively concise separation of the anomalies and the impact that they may have on the patient. Finally, the incidence of visual impairment was found to range from 8% to 71.4%, hence we recommend a full ophthalmological and orthoptic examination as part of the assessment of CFM patients.

Author contributions

All authors made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data. All authors were involved in drafting the article or critically revising it for important intellectual content. Finally, all authors approved the version to be published.

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Competing interests

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

Ethical approval

Not required.

Patient consent

Not required.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2020.03.003.

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