Association of Eyelid Disorders and Ocular Motility Disorders in Pediatric Age: an Epidemiologic Analysis. A Multicenter Retrospective Study.

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Abstract

Purpose: Aim of the study was to evaluate the prevalence and type of strabismus, ptosis and eyelid dynamic disorders features, to assess the prevalence of refractive errors, amblyopia and the association with ocular/systemic syndromes in a cohort of patients.

Methods: Retrospective observational multicenter cohort study enrolling patients with coexisting ocular motility disorders, comitant and incomitant strabismus, ptosis and dynamic eyelid disorders who have never undergone surgery.

Results: 137 out of 19.089 patients were enrolled, of which 97 with uniocular and 40 with binocular disease. Isolated congenital ptosis was observed in 84 patients. A polymalformative syndrome was present in almost one third of cases. There was a slight prevalence of esotropia; most patients were hypermetropic. In monocular disease, myopia affected prevalently older patients, who had worse ptosis margin reflex distance and levator function, and significantly higher astigmatism. Amblyopia occurred in 67.4% of the study sub-population. In monocular disease amblyopia was mild in 25.8%, moderate in 24.2% and severe in 11.3%. In binocular disease was mild in 25%, moderate in 41.7% and severe in 16.7%.

Conclusions: All patients with coexisting eyelid and ocular motility dysfunctions in pediatric age need ophthalmologic and systemic evaluation to accurately assess amblyopia, refractive errors and systemic/ocular disorders.

1. Introduction

Static and dynamic eyelid disorders and ocular motility dysfunctions in pediatric age are often related [1]. Frequency of strabismus among patients with eyelid disorders has been rarely reported, often only concerning congenital ptosis. Griepentrog and Mohny [2] observed strabismus in 18% of children with ptosis, Anderson and Baumgartner [3] in 36% of patients and Thapa [4] in the 27% of patients with congenital ptosis. Furthermore, this association may represent either an isolated feature or associated to several conditions such as congenital cranial dysinnervation disorders (CCDD), ocular syndromes (BPTS), orbital diseases, systemic genetic disorders, central nervous system (CNS) disorders and neurological diseases [1–4].

This association can also be related and can lead to refractive errors and amblyopia [5]. As a matter of facts, in pediatric age, it can significantly affect both visual acuity and normal binocular vision development [6].

A limited number of studies have evaluated the prevalence of eyelid and ocular motility disorders and their association with functional visual deficits and ocular/systemic syndromes. The aim of our multicenter retrospective cross-sectional study is to assess, in a cohort of pediatric patients affected by both strabismus and eyelid dynamic disorders, the prevalence and type of strabismus, the prevalence of refractive errors, the functional visual deficits (amblyopia) and the association with ocular/systemic disorders.

2. Material And Methods

2.1 Study design

This is a retrospective observational multicenter cohort study based on the data from two Italian ocular centers: the Ophthalmology Unit of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy and the Ophthalmology Department of Bambino Gesù IRCCS Pediatric Hospital, Rome.

The study included the medical records of all patients (age 6-16 years) with coexisting ocular motility disorders, comitant and incomitant strabismus, ptosis and eyelid dynamic disorders either in primary or in other gaze positions, who have never been previously surgically treated, afferent at the two tertiary referral centers from January 1, 2017 through December 31, 2019.

All patients with iatrogenic and traumatic eyelid and ocular motility disorders and patients previously surgically treated on eyelids or extraocular muscles were excluded.

Data from ocular and orthoptic examination, including eye motility, cycloplegic refraction, best-corrected visual acuity (BCVA) measurement, upper margin reflex distance (MRD) and levator function (LF) were collected.

MRD and LF were measured for each patient while the patient looked at an examination torch held about half a meter away. A ruler was held against the upper eyelid and the distance between the light reflex and superior eyelid margin was measured in primary position (MRD). When patients failed to show a visible light reflex, as their upper lid covered the pupil foramen, either negative or 0 values were assigned for analytical purposes. When the value was 0, the upper lid margin covered the center of the pupil; when the value was -1, it outstripped the inferior pupil margin. The

LF was evaluated by measuring the excursion in millimeters of the upper eyelid between upgaze and downgaze, fixing the eyebrow.

The categories of the analyzed association were classified as “congenital isolated” and “others”, and included: congenital cranial dysinnervation disorders, genetic diseases, CNS disorders and neurologic diseases, ocular syndromes and orbital diseases. The prevalence of polymalformative syndromes was further assessed. Ptosis features were classified either as bilateral and unilateral ptosis or eyelid asymmetry, whereas strabismus as esotropia, exotropia, vertical squint, and either comitant or incomitant.

Ocular alignment was assessed using prism cover-uncover tests. Cover tests were performed with fixation targets at both distance (6 m) and near (33 cm). The refractive status of all patients was evaluated both before and after cycloplegia using retinoscopy. Refractive status type (Myopia, Hyperopia, and Astigmatism: with the rule and against the rule) and size (diopters) were recorded. Spherical equivalent (SEq) was calculated as the sum of the spherical plus half of the cylindrical power. Myopia, hyperopia and astigmatism were defined as $SEq < 0.5$ diopters (D), $SEq > 0.5$ D and cylindrical error > 1.0 D, respectively. Best Correct Visual Acuity (BCVA) was assessed for right and left eye, when possible, using Lea Symbols charts [7, 8], or using ETDRS charts [9]. During visual acuity testing, all subjects wore spectacles containing the best correction.

Amblyopia was evaluated according to Pediatric Eye Disease Investigator Group (PEDIG) as mild (20/25 to $< 20/40$), moderate (20/40 to 20/80) and severe (20/100 to 20/400) [10]. Family history for eyelid abnormalities, oculomotor disorders and systemic/ocular diseases were also recorded.

The study was carried out with the approval from the Fondazione Policlinico Universitario A. Gemelli IRCCS Ethics Committee (Protocol ID number 0039303/20, ID:3396) and in accordance with 1976 Declaration of Helsinki and its later amendments. A written informed consent for data collection and analysis of collected data from their medical records was obtained from all patients. Photographs were obtained in selected cases with patients' permission.

2.2 Statistical Analysis

All variables included in the study were summarized by descriptive statistics techniques. In depth, qualitative variables were expressed as absolute and percentage frequency. As for quantitative variables, we performed the

Shapiro-Wilk test to assess their distribution. Then, whether normally distributed, they were described as mean and standard deviation (SD), otherwise as median and interquartile range (IQR).

Between groups differences for each parameter considered (strabismus type, categories, refractive error, amblyopia, ptosis features) were assessed, as for qualitative variables, either by the Fisher Exact test or the Chi square test, with Yates correction, as appropriate. Quantitative variables were instead assessed either by one-way ANOVA or Student t test, if normally distributed, otherwise either Mann Whitney U test or Kruskal-Wallis test were applied. A p value <0.05 was considered as statistically significant. All analyses were conducted with STATA software, version 16 (StataCorp. College Station, TX: StataCorp LLC).

3. Results

3.1 General characteristics of the study cohort

During the 3-year study period 137 out of 19.089 patients (0.72%) afferent at the two Ophthalmological Pediatric Centers met the inclusion criteria.

In the same observation period, the total number of patients with eyelid static and dynamic disorders were 292 (1.52%) and the total number of isolated congenital ptosis was 84 (0.44%)

Ninety-seven out of 137 patients had a monocular disease, affecting either right or left eye whereas in 40 cases the disease affected both eyes.

Overall median age was 12 years (IQR 7-16 yrs.). Patients were also homogeneously distributed for sex (47.4% M vs. 52.6% F), both overall and between groups.

Among systemic disorders the less prevalent were ocular syndromes and orbital diseases (6%), whilst in almost one third there was a polymalformative syndrome associated (28.5%). Types of strabismus were almost equally distributed, with a slight prevalence of esotropia (37.2%, n=51). In addition, most patients were hypermetropic (73.7%, n=101).

Patients with disease affecting both eyes were characterized by a significantly higher strabismus angle deviation for distance (p=0.039) and for near (p=0.023). As well, we observed a significantly higher prevalence of comitant strabismus deviation (p=0.021) and ptosis familiar history (p=0.008) among subjects with both eyes affected. Levator function was indeed significantly lower in this subset of patients (median 8 vs 17; p<0.001). All characteristics of the study population are described in Table 1.

Each characteristic of interest in the two subgroups was further separately analysed.

3.2 Strabismus

Strabismus was classified as follows: esotropia, exotropia and vertical squint.

Patients with monocular disease assessment showed that ptosis onset occurs significantly later in those with vertical squint (median 6 moths vs.1 in exotropic and esotropic patients, p=0.010). An association instead emerged as for what concerns strabismus onset (p=0.083), which occurred much more lately in those with vertical squint.

As regards ptosis features, all patients with vertical squint had unilateral ptosis, with the congenital one much more prevalent (83.9% vs. 51.4% in esotropia and 75.9% in exotropia; p=0.010).

Other relevant findings concern the refractive error value, significantly higher in those with esotropia (median 2.5 vs 1.75 in exotropia and 2 in vertical squint; $p=0.044$), whilst BCVA was less evaluable in patients with esotropia (48.6% vs, 65.5% vs. 77.4%; $p=0.047$).

Looking at binocular disease a similar finding was observed as for vertical strabismus and an association with a younger age in patients with esotropia resulted (median 10 yrs. vs. 16 yrs in exotropia and 13 yrs in vertical squint; $p=0.073$). Finally, patients with esotropia have shown higher values of MRD (3 mm vs 1 mm in the other two categories; $p=0.081$). All data are described in Table 2.

3.3 Ptosis features

We thus analysed patients according to ptosis features, either unilateral or bilateral and, within these categories, congenital ptosis or eyelid asymmetry.

As regards patients with monocular disease, we observed that vertical strabismus was significantly higher among patients with unilateral congenital ptosis ($p=0.011$).

A significantly higher prevalence of esotropia occurred in patients with unilateral eyelid asymmetry ($p=0.010$). In the same subgroup MRD (median 4mm vs. 3mm; $p<0.001$) and levator function (median 18mm vs. 16mm; $p<0.001$) were significantly higher than among those with congenital ptosis.

Looking at patients with both eyes affected a similar finding was observed: the MRD (median 4mm vs. 1mm; $p<0.001$) and the LF (median 18mm vs. 8mm; $p<0.001$) were significantly higher in patients with bilateral eyelid asymmetry.

Conversely, astigmatism value was significantly lower in this subset of patients (median 0.75 vs. 2; $p=0.026$). An association instead emerged for a slightly higher refractive error in the group with eyelid asymmetry ($p=0.060$), and for a higher strabismus angle deviation for near, in the group with congenital ptosis ($p=0.093$). All data are reported in Table 3.

3.4 Refractive errors

Refractive error was classified as myopic, hypermetropic and anisometropic.

In patients with monocular disease, older patients were significantly more myopic (median 14.5 years vs. 10 hypermetropic and 11 anisometric, $p=0.005$). Moreover, refractive error was significantly lower in myopic subjects, even though such result is affected by the small sample size of anisometropic patients.

Moreover, in this subgroup of patients, strabismus onset occurred significantly later in myopic subjects (median 6 months vs. 1, $p<0.001$). A comparable finding was also observed for ptosis onset. Myopic subjects were also characterized by a significantly higher prevalence of ptosis familiar history (60% vs. 6.7%, $p=0.001$) and by a lower refractive error (median -3 vs. 2.5, $p<0.001$). Conversely, both MRD (median 1mm vs. 2mm, $p=0.003$) and LF (median 3mm vs. 14mm, $p<0.001$) were significantly lower among myopic patients. A significantly higher astigmatism value among myopic patients was observed (median 3 vs. 1, $p=0.003$). All data are shown in Table 4.

3.5 Diseases Categories

For what concerns categories, we run all the categories grouped through the isolated one, in order to minimize the bias due to small sample sizes of the single subgroups.

Looking first at monocular disease, we observed a significantly higher prevalence of associated polymalformative syndromes in the isolated category (37.8% vs. 13%, $p=0.026$). A suggestive association instead emerged, with a higher prevalence of incomitant strabismus deviation type (56.8% vs. 34.8%, $p=0.066$) and a higher mild amblyopia, in patients with other diseases (50% vs. 17.4%, $p=0.060$).

Among patients with binocular disease, indeed, patients of the isolated category had a significantly higher prevalence of strabismus familiar history (50% vs. 5.6%, $p=0.043$). There was also an association with higher MRD in this subgroup (median 3mm vs. 1mm, $p=0.064$). All data are reported in Table 5.

3.6 Amblyopia

Sixty-two patients with monocular disease were assessed for the visual acuity vs. 24 with binocular disease. Fifty-one uncooperative patients (37.2%) were not assessed. Amblyopia was reported in 58 out of 86 patients (67.4%).

Thirty-eight out of 62 patients with monocular disease were diagnosed as amblyopic (61.3%) according to Pediatric Eye Disease Investigator Group (PEDIG). Of the 62 assessed patients 16 (25.8%) were diagnosed as Mild, 15 (24.2%) as Moderate and 7 (11.3%) as severe. Twenty-four patients (38.7%) had not shown amblyopia in the affected eye.

Among the 24 patients with binocular disease assessed, amblyopia was diagnosed in 60% of the cases. Six patients (25.0%) were diagnosed as mild, 10 (41.7%) as moderate and 4 (16.7%) as severe. Four patients (16.7%) had not assessed as amblyopic in the affected eyes.

A severe amblyopia was assessed in 42.9% of the patients with monocular disease and the 33.3% of the patients with moderate amblyopia presented polymalformative syndromes ($p=0.015$). All data are reported in Table 6.

4. Discussion

Over a 3-year study period, this multicenter study analyzed 137 out of 19,089 patients (0.72%) afferent at the two Ophthalmological Pediatric Centers. The overall prevalence of isolated congenital ptosis was 0.44% (84 out of 19,089 patients), of whom 27 (32.1%) were associated with ocular motility disorders. The reported prevalence of strabismus associated with congenital ptosis ranges from 18–36%, [1, 2, 3, 4] which is a much higher prevalence than in the general population [11].

In about one third of cases there was a accompanying diagnosis of polymalformative syndrome. The binocular type shows a significantly higher prevalence of ptosis familiar history, comitant strabismus, significant higher strabismus angle deviation and lower levator function values.

Regarding strabismus type (esotropia, exotropia, vertical squint), congenital unilateral ptosis was prevalent in patients with vertical squint. Some Authors suggested that strabismus could be secondary to a disruption of binocularity by the ptotic eyelid [12].

On the other hand, as for congenital ptosis associated with vertical strabismus it would be reasonable to suppose that a prenatal insult or maldevelopment of the third cranial nerve could play an important role [13, 14]. Moreover, according to known literature, refractive error value was significantly higher in patients with esotropia [15].

As for ptosis features, we observed a significantly higher prevalence of esotropia and mild ptosis, as well as a good levator function in patients with unilateral and bilateral eyelid asymmetry. These data are mainly related to the clinical features of Type I Duane Retraction Syndrome [16].

With regard to refractive error features, older patients with monocular disease were significantly more myopic, and had a significantly worse ptosis MRD and LF, as well as higher astigmatism value. Several authors reported more severe refractive errors in moderate or severe ptosis. Zeng et al. reported a higher frequency of hyperopia and a lower axial length – corneal radius (AL/CR) ratio in case of severe ptosis, suggesting a delay in the growth of the eye [17]. Huo L et al. instead deemed that long-standing congenital ptosis might produce myopia [18]. The refractive modifications were also related to a mechanic effect of ptotic eyelid on ocular surface that reshapes the corneal surface [19;20]. Our data confirm a mechanical and deprivational effect of moderate and severe eyelid ptosis, which can lead to refractive changes.

The monocular isolated association, as compared with the other categories, is significantly associated with polymalformative syndromes (37.8% vs. 13%, $p=0.026$) and more often shows an incomitant strabismus deviation.

Amblyopia occurred in the 67.4% of the assessed subpopulation. In monocular disease the 25.8% was diagnosed as mild, the 24.2% as moderate and 11.3% as severe (vs. the 25%, 41.7% and 16.7% in those with binocular disease). Amblyopia estimated prevalence in the general population ranges from the 2.5–5.6% [21, 22]. The reported prevalence of amblyopia in patients with ptosis and ptosis and strabismus is 7-8 times higher, and it is associated to a higher prevalence of refractive errors and to a not alternating strabismus [11, 23–25].

5. Conclusions

To the best of our knowledge, this is the first study investigating the relation of eyelids and ocular motility disorders. Eyelid static and dynamic disorders and ocular motility disorders are often related. These patients thus need a careful ophthalmologic and systemic evaluation due the high prevalence of amblyopia, refractive errors and systemic/ocular associated disorders.

Declarations

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due the common policy of our institution, but are available from the corresponding author on reasonable request.

Disclosures

The authors declare no conflict of interests. This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit sectors.

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Tables

Table 1. General characteristics of the study population (n=137).

	Overall (n=137)	Monocular Disease (n=97)	Bi-ocular Disease (n=40)	p
Age (yrs.)	12 [7 – 16]	12 [7 – 16]	13 [6.5 – 16]	0.827
Sex				0.701
<i>M</i>	65 (47.4)	45 (46.4)	20 (50)	
<i>F</i>	72 (52.6)	52 (53.6)	20 (50)	
Categories				0.004
<i>Congenital cranial dysinnervation disorders</i>	25 (18.2)	23 (23.7)	2 (5)	
<i>Isolated</i>	27 (19.7)	23 (23.7)	4 (10)	
<i>Genetic</i>	37 (27)	23 (23.7)	14 (35)	
<i>CNS disorders and neurological diseases</i>	38 (27.7)	24 (24.7)	14 (35)	
<i>Ocular syndromes and orbital diseases</i>	10 (7.3)	4 (4.1)	6 (15)	
Categories				0.110
<i>Isolated</i>	27 (19.7)	23 (23.7)	4 (10)	
<i>Others</i>	110 (80.3)	74 (76.3)	36 (90)	
Polymalphormative syndromes associated	39 (28.5)	31 (32)	8 (20)	0.158
Strabismus type				0.842
<i>Esotropia</i>	51 (37.2)	37 (38.1)	14 (35)	
<i>Exotropia</i>	43 (31.4)	29 (29.9)	14 (35)	
<i>Vertical squint</i>	43 (31.4)	31 (32)	12 (30)	
Strabismus angle deviation distance	14 [6 – 30]	14 [4 – 25]	20 [10 – 30]	0.039
Strabismus angle deviation near	14 [6 – 30]	14 [6 – 25]	20.5 [10 – 33.75]	0.023
Vertical strabismus	0 [0 – 5]	0 [0 – 5]	0 [0 – 3.75]	0.771
Strabismus onset	2 [1 – 6]	2 [1 – 14.3]	1 [1 – 6]	0.311
Strabismus familiar history	7 (5.1)	3 (3.1)	4 (10)	0.214
Strabismus deviation type				0.021
<i>Comitant</i>	75 (54.7)	47 (48.5)	28 (70)	
<i>Incomitant</i>	62 (45.3)	50 (51.5)	12 (30)	
Ptosis familiar history	12 (8.8)	4 (4.1)	8 (20)	0.008
Ptosis features				<0.001
<i>Bilateral-ptosis</i>	34 (24.8)	-	34 (85)	
<i>Bilateral eyelid asymmetry</i>	6 (4.4)	-	6 (15)	
<i>Unilateral-ptosis</i>	67 (48.9)	67 (69.1)	-	

<i>Unilateral eyelid asymmetry</i>	30 (21.9)	30 (30.9)	-	
Ptosis MRD (mm)	3 [1 – 4]	3 [2 – 4]	1 [1 – 3]	<0.001
Ptosis onset	2 [1 – 6]	2 [1 – 6]	1 [1 – 6]	0.715
Levator function	16 [10–18]	17 [14 – 18]	8 [4.25 – 15]	<0.001
Refractive error				0.658
<i>Myopic</i>	34 (24.8)	24 (24.7)	10 (25)	
<i>Hypermetropic</i>	101 (73.7)	71 (73.2)	30 (75)	
<i>Anisometropic</i>	2 (1.5)	2 (2.1)	-	
Refractive error	2.25 [-0.5 – 3]	2.25 [-0.5 – 3.13]	2.25 [-0.38 – 2.94]	0.589
Amblyopia*				0.187
<i>None</i>	28 (32.6)	24 (38.7)	4 (16.7)	
<i>Mild</i>	22 (25.6)	16 (25.8)	6 (25)	
<i>Moderate</i>	25 (29.1)	15 (24.2)	10 (41.7)	
<i>Severe</i>	11 (11.8)	7 (11.3)	4 (16.7)	
Fixing eye				0.581
<i>Right</i>	60 (43.8)	44 (45.4)	16 (40)	
<i>Left</i>	44 (32.1)	32 (33)	12 (30)	
<i>Alternative fixation</i>	33 (24.1)	21 (21.6)	12 (30)	
Is astigmatism evaluable?	79 (57.7)	57 (58.8)	22 (55)	0.685
Astigmatism value	0.5 [0 – 1]	0.5 [0 – 1]	0.5 [0 – 2]	0.517
Is BCVA evaluable?	85 (62)	61 (62.9)	24 (60)	0.752
BCVA Ptosis	0.1 [0 – 0.45]	1. [0 – 0.35]	0.3 [0.1 – 0.68]	0.040
M: Male; F: Female; CNS: Central Nervous System; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity; * Others: congenital cranial dysinnervation disorders, Genetic, CNS disorders/neurological diseases, Ocular syndromes/orbital diseases. ** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR). Significant data are in bold , suggestive p-values in <i>italic</i> .				

Table 2. Association between strabismus type and general and clinical characteristics in the study cohort, according to patients' subgroups (n=137).

	MONOCULAR DISEASE (n=97)				BINOCULAR DISEASE (n=40)			
	Esotropia (n=37)	Exotropia (n=29)	Vertical squint (n=31)	p	Esotropia (n=14)	Exotropia (n=14)	Vertical squint (n=12)	p
Age (yrs.)	12 [7–16]	10 [7–16]	12 [10–15]	0.577	10 [6–14]	16 [3–17]	13 [12–17]	0.073
Sex				0.713				0.123
<i>M</i>	19 (51.4)	12 (41.4)	14 (45.2)		10 (71.4)	6 (42.9)	4 (33.3)	
<i>F</i>	18 (48.6)	17 (58.6)	17 (54.8)		4 (28.6)	8 (57.1)	8 (66.7)	
Categories				0.353				0.433
<i>Isolated</i>	6 (16.2)	9 (31)	8 (25.8)		2 (14.3)	0 (0.0)	2 (16.7)	
<i>Others*</i>	31 (83.8)	20 (69)	23 (74.2)		12 (85.7)	14 (100)	10 (83.3)	
Polymalphormative syndromes associated	13 (35.1)	9 (31)	9 (29)	0.858	2 (14.3)	2 (14.3)	4 (33.3)	0.427
Strabismus angle deviation distance	15 [5 – 22.5]	12 [5 – 27.5]	12 [0 – 25]	0.660	20 [10 – 25]	20 [8 – 30]	20 [10 – 35]	0.936
Strabismus angle deviation near	14 [6 – 25]	14 [7 – 19]	10 [0 – 20]	0.296	25 [10 – 30]	15 [8 – 30]	23 [10 – 55]	0.676
Vertical strabismus	0 [0 – 0]	0 [0 – 0]	10 [5 – 16]	<0.001	0 [0 – 0]	0 [0 – 0]	18 [5 – 40]	<0.001
Strabismus onset	2 [1 – 6]	2 [1 – 34.8]	6 [1 – 48]	0.083	1 [1 – 6]	1 [1 – 108]	4 [1 – 6]	0.746
Strabismus familiar history	-	2 (6.9)	1 (3.2)	0.275	2 (14.3)	2 (14.3)	0 (0.0)	0.524
Ptosis familiar history	1 (2.7)	2 (6.9)	1 (3.2)	0.665	2 (14.3)	6 (42.9)	0 (0.0)	0.019
Strabismus deviation type				0.181				0.265
<i>Concomitant</i>	17 (45.9)	18 (62.1)	12 (38.7)		12 (85.7)	8 (57.1)	8 (66.7)	
<i>Incomitant</i>	20 (54.1)	11 (37.9)	19 (61.3)		2 (14.3)	6 (42.9)	4 (33.3)	
Ptosis features	-	-	-	0.010				0.182
<i>Bilateral ptosis</i>	-	-	-		10 (71.4)	12 (85.7)	12 (100)	
<i>Bilateral eyelid asymmetry</i>	19 (51.4)	22 (75.9)	26 (83.9)		4 (28.6)	2 (14.3)	0 (0.0)	
<i>Unilateral ptosis</i>	18 (48.6)	7 (24.1)	5 (16.1)		-	-	-	

<i>Unilateral eyelid asymmetry</i>								-
Ptosis MRD (mm)	3 [2 – 4]	3 [2 – 4]	3 [1 – 4]	0.121	3 [1 – 4]	1 [1 – 3]	1 [1 – 2]	0.081
Ptosis onset	1 [1 – 4]	2 [1 – 17.3]	6 [1 – 60]	0.010	1 [1 – 6]	1 [1 – 108]	4 [1 – 6]	0.750
Levator function	18 [15 – 18.5]	16 [12 – 18]	18 [14 – 18]	0.489	15 [3 – 16]	8 [4 – 14]	8 [5 – 14]	0.709
Refractive error				0.242				0.811
<i>Myopic</i>	5 (13.5)	8 (27.6)	11 (35.5)		4 (28.6)	4 (28.6)	2 (16.7)	
<i>Hypermetropic</i>	31 (83.8)	21 (72.4)	19		10 (71.4)	10 (71.4)	10	
<i>Anisometropic</i>	1 (2.7)	-	(61.3)		0 (0.0)	0 (0.0)	(83.3)	
			1 (3.2)				0 (0.0)	
Refractive error	2.5 [2 – 4]	1.75 [-0.13 – 3]	2 [-1 – 3]	0.044	2.55 [-4.00 – 7.00]	1.50 [-2.00 – 2.75]	1.75 [1.0 – 2.5]	0.391
Amblyopia**				0.597				-
<i>None</i>	6 (31.6)	6 (31.6)	12 (50)		2 (25.0)	2 (25.0)	0 (0.0)	
<i>Mild</i>	7 (36.8)	4 (21.1)	5 (20.8)		0 (0.0)	2 (25.0)	4 (50.0)	
<i>Moderate</i>	5 (26.3)	6 (31.6)	4		6 (75.0)	4 (50.0)	0 (0.0)	
<i>Severe</i>	1 (5.3)	3 (15.8)	(16.7)		0 (0.0)	0 (0.0)	4 (50.0)	
			3 (12.5)					
Fixing eye				0.949				0.045
<i>Right</i>	17 (45.9)	12 (41.4)	15 (48.4)		10 (71.4)	2 (14.3)	4 (33.3)	
<i>Left</i>	11 (29.7)	11 (37.9)	10		2 (14.3)	6 (42.9)	4	
<i>Alternate fixation</i>	9 (24.3)	6 (20.7)	(32.3)		2 (14.3)	6 (42.9)	(33.3)	
			6 (19.4)				4 (33.3)	
Is astigmatism evaluable?	18 (48.6)	19 (65.5)	20 (64.5)	0.282	10 (71.4)	6 (42.9)	6 (50.0)	0.289
Astigmatism value	0.25 [0 – 1]	0.5 [0 – 1]	0.75 [0 – 1]	0.726	1.75 [1.00 – 2.00]	1.00 [1.00 – 3.00]	1.75 [0.5 – 2.5]	0.880
Is BCVA evaluable?	18 (48.6)	19 (65.5)	24 (77.4)	0.047	8 (57.1)	8 (57.1)	8 (66.7)	0.848
BCVA Ptosis	0.1 [0 – 0.3]	0.2 [0 – 0.4]	0.05 [0 – 0.38]	0.487	0.45 [0.15 – 0.60]	0.20 [0.05 – 0.55]	0.45 [0.1 – 0.95]	0.790
M: Male; F: Female; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity;								

* Others: congenital cranial dysinnervation disorders, Genetic, CNS disorders/neurological diseases, Ocular syndromes/orbital diseases. ** Amblyopia was analysed on the subgroup of patients for which information was available. *** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR). Significant data are in **bold**, suggestive p-values in *italic*.

Table 3. Association between ptosis features and general and clinical characteristics in the study cohort, according to patients' subgroups (n=137).

	MONOCULAR DISEASE (n=97)			BINOCULAR DISEASE (n=40)		
	Unilateral congenital ptosis (n=67)	Unilateral eyelid asymmetry (n=30)	p	Bilateral congenital ptosis (n=34)	Bilateral eyelid asymmetry (n=6)	p
Age (yrs.)	12 [8 – 16]	10 [7 – 15]	0.159	13 [6 – 16]	14 [10 – 16]	0.648
Sex			0.398			0.661
<i>M</i>	33 (49.3)	12 (40)		16 (47.1)	4 (66.7)	
<i>F</i>	34 (50.7)	18 (60)		18 (52.9)	2 (33.3)	
Categories			0.275			1.000
<i>Isolated</i>	18 (26.9)	5 (16.7)		4 (11.8)	-	
<i>Others*</i>	49 (73.1)	25 (83.3)		30 (88.2)	6 (100)	
Polymalphormative syndromes associated	24 (35.8)	7 (23.3)	0.223	6 (17.6)	2 (33.3)	0.580
Strabismus type			0.010			0.182
<i>Esotropia</i>	19 (28.4)	18 (60)		10 (29.4)	4 (66.7)	
<i>Exotropia</i>	22 (32.8)	7 (23.3)		12 (35.3)	2 (33.3)	
<i>Vertical squint</i>	26 (38.8)	5 (16.7)		12 (35.3)	0 (0.0)	
Strabismus angle deviation distance	12 [4 – 25]	14 [5.5 – 20]	0.888	25 [10 – 30]	10 [6 – 16]	0.047
Strabismus angle deviation near	14 [6 – 25]	13 [6 – 21.3]	0.876	30 [10 – 35]	10 [8 – 16]	<i>0.093</i>
Vertical strabismus	0 [0 – 8]	0 [0 – 0]	0.011	0 [0 – 5]	0 [0 – 0]	0.135
Strabismus onset	2 [1 – 30]	2 [1 – 6]	0.240	1 [1 – 6]	1 [1 – 108]	0.933
Strabismus familiar history	2 (3)	1 (3.3)	0.927	4 (11.8)	0 (0.0)	1.000
Strabismus deviation type			0.500			0.153
<i>Comitant</i>	34 (50.7)	13 (43.3)		22 (64.7)	6 (100)	
<i>Incomitant</i>	33 (49.3)	17 (56.7)		12 (35.3)	0 (0.0)	
Ptosis familiar history	4 (6)	-	0.172	8 (23.5)	0 (0.0)	0.318
Ptosis MRD (mm)	3 [2 – 3]	4 [3 – 4]	<0.001	1 [1 – 2]	4 [4 - 4]	<0.001
Ptosis onset	2 [1 – 13]	1.5 [1 – 6]	0.310	1 [1 – 6]	1 [1 – 108]	0.800
Levator function	16 [12 – 18]	18 [17.8 – 19]	<0.001	8 [4 – 14]	18 [16 - 18]	<0.001
Refractive error			0.457			0.307
<i>Myopic</i>	18 (26.9)	6 (20)		10 (29.4)	0 (0.0)	

<i>Hypermetropic</i>	47 (70.1)	24 (80)		24 (70.6)	6 (100)	
<i>Anisometropic</i>	2 (3)	-		0 (0.0)	0 (0.0)	
Refractive error	2.25 [-0.5 – 3]	2.25 [1 – 3.25]	0.504	1.625 [-0.50 – 2.75]	2.55 [2.25 – 6.50]	<i>0.060</i>
Amblyopia**			0.699			n.a.
<i>None</i>	16 (37.2)	8 (42.1)		0 (0.0)	4 (100)	.
<i>Mild</i>	10 (23.3)	6 (31.6)		6 (30.0)	0 (0.0)	
<i>Moderate</i>	11 (25.6)	4 (21.1)		10 (50.0)	0 (0.0)	
<i>Severe</i>	6 (14)	1 (5.3)		4 (20.0)	0 (0.0)	
Fixing eye			0.167			0.102
<i>Right</i>	33 (49.3)	11 (36.7)		14 (41.2)	2 (33.3)	
<i>Left</i>	23 (34.3)	9 (30)		8 (23.5)	4 (66.7)	
<i>Alternate fixation</i>	11 (16.4)	10 (33.3)		12 (35.3)	0 (0.0)	
Is astigmatism evaluable?	41 (61.2)	16 (53.3)	0.467	18 (52.9)	4 (66.7)	0.673
Astigmatism value	0.5 [0 – 1]	0.4 [0 – 1]	0.523	2.0 [1.0 – 3.0]	0.75 [0.5 – 1.0]	0.026
Is BCVA evaluable?	43 (64.2)	18 (60)	0.694	20 (58.8)	4 (66.7)	1.000
BCVA Ptosis, median [IQR]	0.1 [0 – 0.4]	0.1 [0 – 0.3]	0.624	0.5 [0.1 – 0.7]	-	n.a.
M: Male; F: Female; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity; n.a.: not applicable. * Others: congenital cranial dysinnervation disorders, Genetic, CNS disorders/neurological diseases, Ocular syndromes/orbital diseases. ** Amblyopia was analysed on the subgroup of patients for which information was available. *** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR). Significant data are in bold , suggestive p-values in <i>italic</i> .						

Table 4. Association between type of refractive error and general and clinical characteristics in the study cohort, according to patients' subgroups (n=137).

	MONOCULAR			BINOCULAR			
	Myopic (n=24)	Hypermetric (n=71)	Anisometric (n=2)	p	Myopic (n=10)	Hypermetric (n=30)	p
Age (yrs.)	14.5 [12 – 17]	10 [7 – 15]	11 [7 - /]	0.005	17 [10 – 17]	13 [6 – 16]	0.117
Sex				0.865			0.465
<i>M</i>	10 (41.7)	34 (47.9)	1 (50)		6 (60.0)	14 (46.7)	
<i>F</i>	14 (58.3)	37 (52.1)	1 (50)		4 (40.0)	16 (53.3)	
Categories				0.043			0.556
<i>Isolated</i>	5 (20.8)	18 (25.4)	-		0 (0.0)	4 (13.3)	
<i>Others</i>	19 (79.2)	53 (74.6)	2 (100)		10 (100)	26 (86.7)	
Polymalphormative syndromes associated	6 (25)	24 (33.8)	1 (50)	0.623	0 (0.0)	8 (26.7)	0.165
Strabismus type				0.242			0.811
<i>Esotropia</i>	5 (20.8)	31 (43.7)	1 (50)		4 (40.0)	10 (33.3)	
<i>Exotropia</i>	8 (33.3)	21 (29.6)	-		4 (40.0)	10 (33.3)	
<i>Vertical squint</i>	11 (45.8)	19 (26.8)	1 (50)		2 (20.0)	10 (33.3)	
Strabismus angle deviation distance	16.5 [7 – 30]	12 [4 – 20]	21 [12 - /]	0.270	25 [25– 30]	10 [8 – 30]	0.024
Strabismus angle deviation near	15 [7 – 25]	12 [4 – 25]	19 [8 - /]	0.450	30 [25– 30]	10 [8 – 35]	<i>0.068</i>
Vertical strabismus	0 [0 – 9]	0 [0 – 2]	2.5 [0 - /]	0.296	0 [0 – 0]	0 [0 – 5]	0.805
Strabismus onset	2.5 [1 – 70.3]	2 [1 – 6]	3.5 [1 - /]	0.537	6 [6 – 14]	1 [1 – 6]	<0.001
Strabismus familiar history	-	3 (4.2)	-	0.567	0 (0.0)	4 (13.3)	0.556
Strabismus deviation type				0.352			0.451
<i>Comitant</i>	11 (45.8)	36 (50.7)	-		6 (60.0)	22 (73.3)	
<i>Incomitant</i>	13 (54.2)	35 (49.3)	2 (100)		4 (40.0)	8 (26.7)	

Ptosis familiar history	1 (4.2)	3 (4.2)	-	0.957	6 (60.0)	2 (6.7)	0.001
Ptosis features				0.457			0.307
<i>Bilateral ptosis</i>	-	-	-		10 (100)	24 (80.0)	
<i>Bilateral eyelid asymmetry</i>	-	-	-		0 (0.0)	6 (20.0)	
<i>Unilateral ptosis</i>	18 (75)	47 (66.2)	2 (100)		-	-	
<i>Unilateral eyelid asymmetry</i>	6 (25)	24 (33.8)	-		-	-	
Ptosis MRD (mm)	3 [2 – 4]	3 [2 – 4]	2 [1 - /]	0.561	1 [0 – 1]	2 [1 – 4]	0.003
Ptosis onset	2 [1 – 68.4]	2 [1 – 6]	3.5 [1 - /]	0.483	6 [6 – 138]	1 [1 – 6]	<0.001
Levator function	18 [16 – 18]	16 è14 – 18]	18 [18 – 18]	0.293	3 [3 – 4]	14 [7 – 16]	<0.001
Refractive error	-1 [-2.25 – -0.5]	2.75 [2 – 3.5]	-6.5 [-11 - /]	<0.001	-3 [-4 – -2]	2.50 [1.75 – 3.25]	<0.001
Amblyopia				0.141			-
<i>None</i>	9 (45)	15 (36.6)	-		0 (0.0)	4 (28.6)	
<i>Mild</i>	4 (20)	15 (36.6)	-		0 (0.0)	6 (42.9)	
<i>Moderate</i>	4 (20)	11 (26.8)	-		8 (80.0)	2 (14.3)	
<i>Severe</i>	3 (15)	3 (7.3)	1 (50)		2 (20.0)	2 (14.3)	
Fixing eye				0.500			0.603
<i>Right</i>	8 (33.3)	35 (49.3)	1 (50)		4 (40.0)	12 (40.0)	
<i>Left</i>		20 (28.2)	1 (50)			8 (26.7)	
<i>Alternate fixation</i>	11 (45.8)	16 (22.5)	-		4 (40.0)	10 (33.3)	
	5 (20.8)				2 (20.0)		
Is astigmatism evaluable? n (%)	14 (58.3)	41 (57.7)	2 (100)	0.488	6 (60.0)	16 (53.3)	1.000
Astigmatism value.	0.4 [0 – 1.2]	0.5 [0 – 1]	1.75 [1.5 - /]	0.158	3 [2 – 3]	1.00 [0.75 – 1.75]	0.003
Is BCVA evaluable? n (%)	20 (83.3)	40 (56.3)	1 (50)	0.057	10 (100)	14 (46.7)	0.003
BCVA Ptosis	0.1 [0 – 0.4]	0.1 [0 – 0.3]	1 [1 – 1]	0.263	0.6 [0.6- 0.7]	0.1 [0.0 – 0.3]	0.125
AM: Male; F: Female; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity; IQR: interquartile range							

* Others: congenital cranial dysinnervation disorders, Genetic, CNS disorders/neurological diseases, Ocular syndromes/orbital diseases. ** Amblyopia was analysed on the subgroup of patients for which information was available. *** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR). Significant data are in **bold**, suggestive p-values in *italic*.

Table 5. Association between disease categories and general and clinical characteristics in the study cohort, according to patients' subgroups (n=137).

	MONOCULAR			BINOCULAR		
	<i>Other</i> (n=74)	<i>Isolated</i> (n=24)	p	<i>Isolated</i> (n=4)	<i>Others</i> (n=36)	p
Age (yrs.)	12 [7.8 – 16]	12 [7 – 15]	0.683	10 [6 – 13]	14 [8–16]	0.319
Sex			0.524			1.000
<i>M</i>	33 (44.6)	12 (52.2)		2 (50.0)	18 (50.0)	
<i>F</i>	41 (55.4)	11 (47.8)		2 (50.0)	18 (50.0)	
Polymalphormative syndromes associated	28 (37.8)	3 (13)	0.026	-	8 (22.2)	0.566
Strabismus type			0.353			0.433
<i>Esotropia</i>	31 (41.9)	6 (26.1)		2 (50.0)	12 (33.3)	
<i>Exotropia</i>	20 (27)	9 (39.1)		-	14 (38.9)	
<i>Vertical squint</i>	23 (31.1)	8 (34.8)		2 (50.0)	10 (27.8)	
Strabismus angle deviation distance	13 [4 – 26.3]	14 [6 – 20]	0.812	17 [4 – 30]	20 [10–30]	0.467
Strabismus angle deviation near	12 [4 – 25]	16 [8 – 25]	0.278	20 [4 – 35]	21 [10 – 30]	0.585
Vertical strabismus	0 [0 – 5]	0 [0 – 12]	0.417	0 [0 – 0]	0 [0 – 5]	0.236
Strabismus onset, mean (SD)	2 [1 – 17]	2 [1 – 13]	0.919	6 [6 – 6]	1 [1 – 6]	0.108
Strabismus familiar history	1 (1.4)	2 (8.7)	0.277	2 (50.0)	2 (5.6)	0.043
Strabismus deviation type			0.066			0.297
<i>Comitant</i>	32 (43.2)	15 (65.2)		4 (100)	24 (66.7)	
<i>Incomitant</i>	42 (56.8)	8 (34.8)		-	12 (33.3)	
Ptosis familiar history	4 (5.4)	-	0.590	-	8 (22.2)	0.566
Ptosis features			0.275			1.000
<i>Bilateral-ptosis</i>	-	-		4 (100)	30 (83.3)	
<i>Bilateral eyelid asymmetry</i>	-	-		-	6 (16.7)	
<i>Unilateral ptosis</i>	49 (66.2)	18 (78.3)		-	-	
<i>Unilateral eyelid asymmetry</i>	25 (33.8)	5 (21.7)		-	-	
Ptosis MRD (mm)	3 [2 – 4]	3 [2 – 4]	0.968	3.0 [2.5 – 3.5]	1.0 [1.0 – 3.0]	0.064
Ptosis onset	2 [1 – 9.9]	2 [1 – 6]	0.405	6 [6–6]	1 [1–6]	0.108
Levator function	18 [14 – 18]	16 [15 – 18]	0.608	15 [14 – 15]	8 [4 – 16]	0.221
Refractive error			0.658			0.556

<i>Myopic</i>	19 (25.7)	5 (21.7)	-	10 (27.8)		
<i>Hypermetropic</i>	53 (71.6)	18 (78.3)	4 (100)	26 (72.2)		
<i>Anisometropic</i>	2 (2.7)	-	-	-		
Refractive error	2 [-0.5 – 3]	3 [1 – 3.25]	0.185	2 [1.75 – 2.25]	2.25 [-0.5 – 3.125]	0.928
Amblyopia*			<i>0.060</i>			n.a.
<i>None</i>	21 (45.7)	3 (18.8)	-	4 (16.7)		
<i>Mild</i>	8 (17.4)	8 (50)	-	6 (25.0)		
<i>Moderate</i>	12 (26.1)	3 (18.8)	-	10 (41.7)		
<i>Severe</i>	5 (10.9)	2 (12.5)	-	4 (16.7)		
Fixing eye			0.733			0.031
<i>Right</i>	34 (45.9)	10 (43.5)	4 (100)	12 (33.3)		
<i>Left</i>	23 (31.1)	9 (39.1)	-	12 (33.3)		
<i>Alternative fixation</i>	17 (23)	4 (17.4)	-	12 (33.3)		
Is astigmatism evaluable? n (%)	43 (58.1)	14 (60.9)	0.814	2 (50.0)	20 (55.6)	1.000
Astigmatism value	0.5 [0 – 1]	0.5 [0 – 1]	0.989	0.5 [0.5 – 0.5]	1.75 [1.0 – 2.75]	n.a.
Is BCVA evaluable? n (%)	45 (60.8)	16 (69.6)	0.448	-	24 (66.7)	0.020
BCVA Ptosis	0.1 [0 – 0.4]	0.2 [0.1 – 0.3]	0.306	-	0.3 [0.1 – 0.7]	n.a.
M: Male; F: Female; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity;. * Amblyopia was analysed on the subgroup of patients for which information was available. ** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR). Significant data are in bold , suggestive p-values in <i>italic</i> .						

Table 6. Association between amblyopia and general and clinical characteristics in the study cohort according to patients' subgroups.**, ***

	Amblyopia			
MONOCULAR DISEASE	Absent (n=24)	Mild (n=16)	Moderate (n=15)	Severe (n=7)
Age (yrs.)	12 [8.5 – 16]	12.5 [8.3–18]	11 [8 – 14]	12 [12 – 15]
Sex				
<i>M</i>	8 (33.3)	6 (37.5)	8 (53.3)	1 (28.6)
<i>F</i>	16 (66.7)	10 (62.5)	7 (46.7)	5 (71.4)
Categories				
<i>Isolated</i>	6 (25)	5 (31.3)	4 (26.7)	-
<i>Others*</i>	18 (75)	11 (68.7)	11 (73.3)	7 (100)
Polymalphormative syndromes	-	4 (25)	5 (33.3)	3 (42.9)
Strabismus type				
<i>Esotropia</i>	6 (25)	7 (43.8)	5 (33.3)	1 (14.3)
<i>Exotropia</i>	6 (25)	4 (25)	6 (40)	3 (42.9)
<i>Vertical squint</i>	12 (50)	5 (31.3)	4 (26.7)	3 (42.9)
Strabismus angle deviation distance	12 [0 – 17.5]	16 [8 – 20]	15 [4 – 35]	20 [6 – 30]
Strabismus angle deviation near	8 [4 – 15.5]	14 [7 – 23.3]	20 [8 – 35]	12 [6 – 25]
Vertical strabismus	1 [0 – 8]	0 [0 – 9]	0 [0 – 0]	0 [0 – 5]
Strabismus onset	4.5 [1 – 48]	4 [1 – 110.9]	4 [1 – 30]	6 [1 - 21.5]
Strabismus familiar history	3 (12.5)	-	-	-
Strabismus deviation type				
<i>Comitant</i>	9 (37.5)	8 (50)	9 (60)	4 (57.1)
<i>Incomitant</i>	15 (62.5)	8 (50)	6 (40)	3 (42.9)
Ptosis features				
<i>Bilateral ptosis</i>	-	-	-	-
<i>Bilateral eyelid asymmetry</i>	-	-	-	-
<i>Unilateral ptosis</i>	16 (66.7)	10 (62.5)	11 (73.3)	6 (85.7)
<i>Unilateral eyelid asymmetry</i>	8 (33.3)	6 (37.5)	4 (26.7)	1 (14.3)
Ptosis familiar history	-	-	1 (6.7)	1 (14.3)
Ptosis MRD (mm) *	3 [3 – 4]	3.5 [2.3 – 4]	3 [2 – 4]	2 [1 – 4]
Ptosis onset	3.5 [1 – 57]	2 [1 – 6]	4 [2 – 6]	6 [1 – 21.5]
Levator function	18 [16.3–18.8]	18 [16 – 18]	16 [14 – 18]	16 [10 – 18]

Refractive error				
<i>Myopic</i>	9 (37.5)	4 (25)	4 (26.7)	3 (42.9)
<i>Hypermetropic</i>	15 (62.5)	12 (75)	11 (73.3)	3 (42.9)
<i>Anisometropic</i>	-	-	-	1 (14.2)
Refractive error	1.4 [-0.5 – 2.9]	2.8 [-0.1 – 3.4]	2.5 [-1.25 – 3.25]	-0.5 [-7.5-2.5]
Fixing eye				
<i>Right</i>	11 (45.8)	5 (31.3)	11 (73.3)	4 (57.1)
<i>Left</i>	8 (33.3)	8 (50)	1 (6.7)	3 (42.9)
<i>Alternative fixation</i>	5 (20.8)	3 (18.8)	3 (20)	-
Is astigmatism evaluable?	15 (62.5)	10 (62.5)	9 (60)	5 (71.4)
Astigmatism value	0.5 [0 – 1]	0.63 [0 – 1]	0.5 [0 – 1.25]	1 [0 – 1]
Is BCVA evaluable?	23 (95.8)	16 (100)	15 (100)	7 (100)
BCVA Ptosis	0 [0 – 0]	0.1 [0.1 – 0.2]	0.4 [0.3 – 0.5]	1 [1 – 1]
BINOCULAR DISEASE	Absent	Mild	Moderate	Severe
	(n=4)	(n=6)	(n=10)	(n=4)
Age (yrs.)	13 [10 – 16]	13 [12 – 16]	15 [10 – 17]	18 [17 – 18]
Sex				
<i>M</i>	2 (50)	4 (66.7)	6 (60)	-
<i>F</i>	2 (50)	2 (33.3)	4 (40)	4 (100)
Categories				
<i>Isolated</i>	-	-	-	-
<i>Others*</i>	4 (100)	6 (100)	10 (100)	4 (100)
Polymalphormative syndromes association	-	2 (100)	-	-
Strabismus type				
<i>Esotropia</i>	2 (50)	-	6 (60)	-
<i>Exotropia</i>	2 (50)	2 (33.3)	4 (40)	-
<i>Vertical squint</i>	0	4 (66.7)	-	4 (100)
Strabismus angle deviation distance	8 [6 – 10]	30 [10 – 35]	25 [25 – 30]	35 [0 – 70]
Strabismus angle deviation near	9 [8 – 10]	40 [10 – 55]	30 [25 – 30]	35 [0 – 70]
Vertical strabismus	0 [0 – 0]	5 [0 – 50]	0 [0 – 0]	35 [30 – 40]
Strabismus onset	55 [1 – 108]	1 [1 – 6]	6 [6 – 6]	7 [1 – 14]
Strabismus familiar history	-	-	-	-

Strabismus deviation type				
<i>Comitant</i>	4 (100)	4 (66.7)	6 (60)	-
<i>Incomitant</i>	-	2 (33.3)	4 (40)	4 (100)
Ptosis features				
<i>Bilateral ptosis</i>	-	6 (100)	10 (100)	4 (100)
<i>Bilateral eyelid asymmetry</i>	4 (100)	-	-	-
<i>Unilateral ptosis</i>	-	-	-	-
<i>Unilateral eyelid asymmetry</i>	-	-	-	-
Ptosis familiar history	-	-	6 (60)	-
Ptosis MRD (mm) *	4.0 [3.5 – 4.5]	1.0 [1.0 – 3.0]	1.0 [0.0 – 1.0]	1.0 [0.5 – 1.5]
Ptosis onset	55 [1 – 108]	1 [1 – 6]	6 [6 – 6]	69 [1 – 138]
Levator function	17 [16 – 18]	14 [5 – 18]	3 [3 – 4]	6 [2 – 9]
Refractive error				
<i>Myopic</i>	-	-	8 (80)	2 (50)
<i>Hypermetropic</i>	4 (100)	6 (100)	2 (20)	2 (50)
<i>Anisometropic</i>	-	-	-	-
Refractive error	2.4 [2.3 – 2.6]	1.0 [0.0 – 1.5]	-3.0 [-4.0 – -2.0]	1.0 [-0.5 – 2.5]
Fixing eye				
<i>Right</i>	2 (50)	2 (33.3)	4 (40)	2 (50)
<i>Left</i>	2 (50)	-	2 (20)	2 (50)
<i>Alternative fixation</i>	-	4 (66.7)	4 (40)	-
Is astigmatism evaluable?	2 (50)	2 (33.3)	8 (80)	2 (50)
Astigmatism value	0.75 [0.5 – 1.0]	2.5 [2.5 – 2.5]	2.50 [1.75 – 3.00]	2.0 [1.0 – 3.0]
Is BCVA evaluable?	4 (100)	6 (100)	10 (100)	4 (100)
BCVA Ptosis	0 [0 – 0]	0.1 [0.1 – 0.1]	0.6 [0.3 – 0.6]	0.95 [0.85–1]
M: Male; F: Female; MRD: Margin Reflex Distance; BCVA: Best Corrected Visual Acuity;				
* Others: congenital cranial dysinnervation disorders Genetic CNS disorders/neurological diseases Ocular syndromes/orbital diseases. ** Amblyopia was analysed on the subgroup of patients for which information was available. *** Qualitative variables are expressed as absolute and percentage frequency quantitative data as median and interquartile range (IQR)				