·Clinical Research·

Essential infantile esotropia with inferior oblique hyperfunction: long term follow-up of 6 muscles approach

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Abstract

• AIM: To evaluate long term follow-up (10y) of 6 muscle surgical approach in essential infantile esotropia (EIE).

• METHODS: A 6 muscle approach to EIE was retrospectively evaluated in patients with inferior oblique (IO) hyperfunction and lateral rectus (LR) pseudoparalysis, who underwent surgery at different ages. Different clinical characters were analyzed pre- and postoperatively, in patients who underwent a 6 muscles approach ≤4 years of age. All patients underwent a multiple muscles approach: bilateral medial recti (MR) recession (4-5 mm), bilateral LR resection (lower than 7 mm) and bilateral IO recession and anteroposition. Of 108 children with preoperative angle ≥+30 prism diopters (PD) and IO hyperfunction were selected from larger cohort of patients (*n*=213, 103 females and 110 males) after excluding patients with: angle variability, who underwent reoperation and with incomplete follow up. Preoperative assessment and complete orthoptic examination were performed. Follow-up was performed 3mo, 2, 5 and 10y after surgery. Statistical analysis was performes using SAS statistical software package (version 9.1, SAS Institute Inc., Cary, NC, USA).

• RESULTS: Ten years follow up data analysis showed the following percentage of orthotropic patients: (0 PD): 3mo, 22.2%; 2y, 16.7%; 5y, 25.0% and 10y, 27.8%. A slight, significant (*P*<0.01), increase of 2y follow up residual deviation was found when compared to 3mo one. Stationary surgical results is reported during time, with a trend of mean residual deviation reduction (*P*=0.04).

• CONCLUSION: Our results confirm the reliability of multiple muscles surgical approach in the treatment of patients affected by EIE with OI hyperfunction.

• **KEYWORDS:** essential infantile esotropia; surgical treatment; follow-up
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INTRODUCTION

Essential infantile esotropia (EIE, incidence ranges from 1% to 0.1%[1-3]) is generally present before 6 months of age, exhibiting constant angle greater than 30 prism diopters (PD) low hypermetropia and medium grade amblyopia. EIE usually shows latent nystagmus, dissociated vertical deviation (DVD) and reduced binocular vision. Other clinical parameters may also be associated, such as excessive adduction, abduction restriction, oblique muscles dysfunctions and cross-fixation. EIE require extensive ophthalmological and orthoptic examinations to diagnose or rule out the presence of amblyopia, establish strabismus type, evaluate and define deviation angle, analyze sensory status [for unilateral or alternating exclusion, central suppression, anomalous retinal correspondence, binocular single vision (BSV)] and stereopsis.

EIE managmentis without doubt, based on surgery. However, surgical intervention needs the presence of several conditions: horizontal deviation stability, estimation of vertical deviation, absence of accommodative factors, and presence of alternating fixation (spontaneous or re-educated and satisfactory patient cooperation to set up an appropriate operative program.

In cases of small deviation angles, the traditional surgical approach is medial recti (MR) bilateral recession, associated, if needed, with lateral rectus (LR) resection.

Concerning large-angle esotropia (ET), surgical technique is still controversial. In these patients, surgery can be performed on 3 muscles, with double MR recession and unilateral LR resection or on 4 muscles (double MR recession with bilateral resection of the LR). In children presenting EIE associated with LR pseudoparalysis and inferior oblique (IO) hyerfunction, it is also possible to perform a 6 muscles approach in a single surgical session (bilateral MR recession, bilateral LR resection, bilateral IO recession and anteriorization).

The aim of our study was to evaluate long term follow-up (10y) of 6 muscle surgical approach in EIE.

SUBJECTS AND METHODS

A retrospective data analysis of 108 patients who underwent a 6 muscles approach ≤4 years of age was performed. Setting of the study was the Pediatric Ophthalmology Department of two Teaching Hospitals (University of Salerno and University of Naples, Italy) and a private practice (Naples, Italy). Patients were follow-up in these centers before and/or after surgery. Data were retrospectively collected in 2014-2015. Surgeries were performed between 2002 and 2005 (at Naples University). Informed consent was obtained prior to surgery from the parents, after complete information concerning peri-operative and post-operative risks. All surgical procedures were conducted according to the Declaration of Helsinki.

All selected patients showed the following characteristics: preoperative stable angle ≥+30 PD, bilateral IO hyperfunction, squint onset before 6 months of age, surgery performed ≤4 years of age, hyperopia lower than 3 D, absence of associated ocular or central nervous system abnormalities.

The exclusion criteria: significant difference of horizontal deviation angle (≥15 PD) among 3 consecutive examination before surgery (defined as angle variability), previous extraocular muscles surgery, reoperation and uncomplete data.

All patients underwent complete ophthalmological evaluation: anterior chamber, gonioscopy and fundus oculi were examined in order to exclude retinal or dioptric media abnormality and assessing a differential diagnosis, cycloplegic refraction was evaluated by retinoscopy to rule out significant preoperative hypermetropia. Spherical equivalent (SE) was evaluated during follow-up at last examination.

Re-educated alternating fixation was defined as an alternating fixation obtained after patching treatment, in patients who previously showed marked fixation of one eye. Moderate amblyopia was defined as a best corrected visual acuity (BCVA) ranged from 0.2 to 0.5 logarithm of the minimum angle of resolution (logMAR). All patients underwent from 1 to 3 extensive orthoptic evaluations in order to assess angle of deviation stability, muscles function, fixation and sensory state.

Anamnestic data were collected to point out familiarity with strabismus or systemic/metabolic disease. Horizontal angle deviation was measured after total correction of refractive error, if present, using Krimsky test (at distance and at near) and, in cooperative children, using cover-test (cover, cover-uncover and alternating cover test). The characteristics of esotropia [right eye (RE) or left eye (LE) prevalence; alternating esotropia] and the stability of angle deviation were assessed. Occlusion treatment (unilateral or alternating) was prescribed when required. Eye movements (ductions and versions) were analyzed. Bilateral LR pseudoparalysis was defined as abduction deficit recordable only during version examination; eye movements were within the normal limits during ductions. On the other hand, bilateral LR abduction limitation was considered as an uncomplete movement also by examining ductions.

IO hyperfunction (up-shoot) was graded in all patients, using an arbitrary scale from (+) to (++++), where the greatest number of + indicated the intensity of the up-shoot; to underline the differences between eyes, both RE and LE up-shoots were reported,

Alphabetical variations (V or A), DVD, abnormal head position (AHP), amblyopia, cross-fixation and nystagmus were recorded.

Binocular vision was preoperatively investigated using Lang's II and Titmus test; at last follow-up Lang II, Titmus and Worth 4 light tests were used. Unilateral or alternating exclusion, BSV and stereopsis data were reported.

All patients underwent surgery under general anesthesia, within the first 4 years of life, a 6 muscles approach: bilateral MR recession (4-5 mm), bilateral LR resection (<7 mm), bilateral IO recession and anteroposition. MR recessions and LR resections were all performed by limbal incision with direct scleral fixation. IO recession + anteriorization was performed. IO recession entity ranges, in our data, from 4 to 9 mm (the greater upshoot related to the greater recession entity); IO scleral suture was attached between LR and IO, at the equator level.

All patients were discharged the day after surgery. Patients were treated with steroid-antibiotic topical eye drops, 3 times a day, for 20d following their operation and systemic antibiotics for 5d after surgery.

Follow-up was performed after surgery: 3mo, 2, 5 and 10y.

Post-operative success was defined by the following deviation criteria: orthotropic (0 PD); small angle residual ET (between 0 and +10 PD); small angle secondary exotropia (XT) (between 0 and -10 PD); ET (> +10 PD); XT (<-10 PD).

Statistical Analysis A two-tailed paired *t*-test was performed to compare baseline distance and near deviation and those at 3mo, 2, 5 and 10y after surgery. Pearson's correlation was also applied in order to examine a possible relationship between the muscles' recession/resection and the residual deviation and the relationship between residual deviation and refractive error. For all analyses, a conservative *P* value of <0.05 was considered as statistically significant. SAS statistical software package (version 9.1, SAS Institute Inc., Cary, NC, USA) was used.

Table 1 Millimeter amount of surgical approach

Surgical approach	RE				LE			
	MR rec	Conj rec	LR res	IO rec	MR rec	Conj rec	LR res	IO rec
$\bar{x} \pm s$ (mm)	4.51±0.57	4.13±0.71	6.59±0.69	6.34±1.11	4.52±0.51	4.16±0.79	6.83±0.65	6.89±1.11
Range (min, max)	3, 6	4, 8	4, 8	4, 8	4, 5,5	4, 8	5, 8	5, 9
Median	3	4	7	7,5	4,5	4	7	7

RE: Right eye; LE: Left eye; Rec: Recession; Res: Resection; MR: Medial recti; LR: Lateral rectus; IO: Inferior oblique; Conj: Conjuctiva.

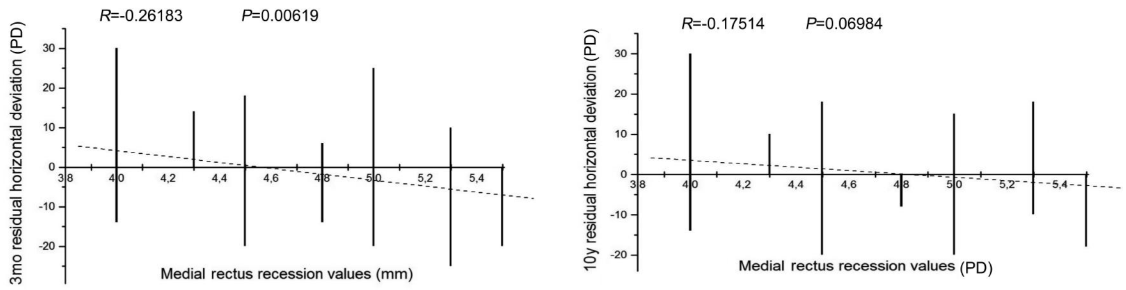

Figure 1 Correlation between MR recession A: Three months residual horizontal deviation (PD); B: Ten years residual horizontal deviation (PD).

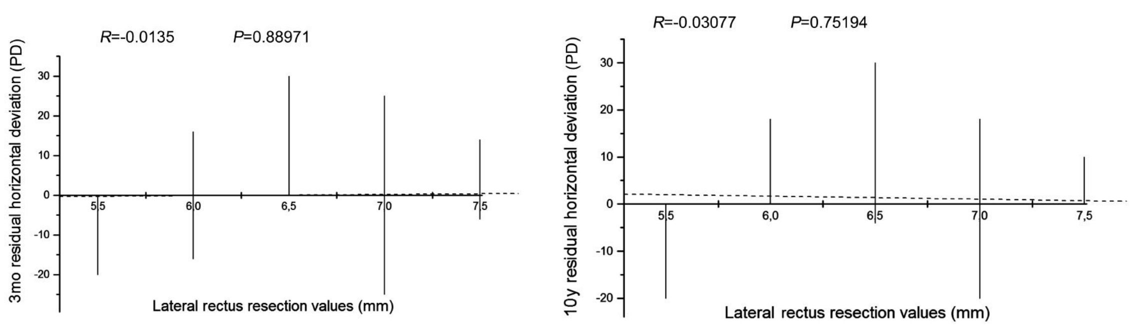

Figure 2 Correlation between LR resection A: Three months residual horizontal deviation (PD); B: Ten years residual horizontal deviation (PD).

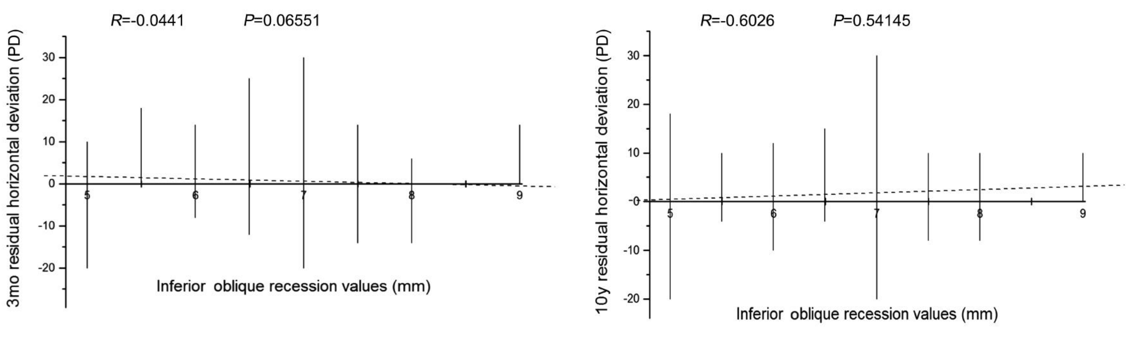

Figure 3 Correlation between IO recession A: Three months residual horizontal deviation (PD); B: Ten years residual horizontal deviation (PD).

RESULTS

One hundred and eight children (60 females, 48 males) were enrolled. Mean age at surgery was 2.86±0.83y (range 2 to 4y).

All children were operated by a single surgeon (Magli A) using a 6 muscles approach (see subjects and methods section), the same orthoptic team were responsible for the entire follow-up.

Patients were preoperatively divided into two groups: small angle esotropia (≤ 40 PD) and large angle esotropia (> 40 PD).

Upshoot was recorded in all 108 patients. Sixty-six patients showed an upshoot +, 33 patients were ++ (6 RE>LE and 27 LE>RE), and 9 patients were +++.

Absence of abduction limitation/LR pseudoparalysis was reported in 9 patients, bilateral LR pseudoparalisis in 36 patients, and bilateral abduction limitation in 63 patients. Table 1 showed surgical procedure technical data (resection/ recession millimeters).

Figures 1, 2 and 3 show correlation between MR recession, LR resection, IO recession and residual deviation at first and last follow-up.

Results shows a significant correlation between mean MR recession amount and postoperative deviation (at 3mo) (P<0.05). No significant correlations between MR recession amount and 10y post-operative horizontal deviation was reported. Nevertheless, a trend of significance has to be mentioned. In addition, no significant correlation between mean LR resection amount and postoperative horizontal deviation was reported (at 3mo and 10y). Similarly, no significant correlations between mean IO recession amount, 3mo and 10y horizontal residual deviation was reported. Table 2 shows residual deviation distribution during follow up.

A higher incidence of residual ET compared to secondary XT during follow-up was reported, except for 3mo one. This finding suggests that multiple muscles procedure is not necessarily related to surgical overcorrection. Ten years follow-up residual deviation incidence was 25% (11.1% secondary XT +13.9% residual ET), 12 patients showed an ET >+15 PD and 9 patients showed an XT >18 PD. Slight, but significant increase of deviation was found when 2y follow-up mean deviation was compared to 3mo one (P<0.01). Surgical result showed no significant modification over time; a slight trend of reduction of residual deviation during follow up (P=0.04) was reported,

Table 3 and Figure 4 shows the angle of deviation follow up of small (≤40 PD) and large (>40 PD) angle esotropia group. No significant differences were found when small and large angle mean residual horizontal and vertical deviation values progression were compared (P>0.11).

Interestingly, significant correlation was found when individual MR recession amount values and residual deviation at 3mo and 10y follow up of small angle esotropia group were plotted (P<0.0001). No significant correlations were found when amount of surgery values and residual deviation values of large angle patients during follow up were plotted.

Mean values of vertical deviation 3mo after surgery showed a trend of reduction at 2y follow up (P<0.01); no significant changes were reported at 5 and 10y follow up. Table 4 shows vertical deviation angle distribution.

This finding is suggestive for a correlation, mainly in small angle EIE, between a greater MR recession amount and postoperative consecutive XT.

Performing multiple muscles procedure, the risk of ischemia of anterior segment has to be considered. As described by Wright[4], the anterior segment is fed by seven anterior ciliary arteries and two long posterior ciliary arteries, 50% of perfusion comes from posterior ciliary arteries, while 50% from anteriorciliary vessels. Two anterior ciliary arteries course through medial, superior and inferior rectus, while LR muscle has only one artery. Consequently, the detachments of a rectus muscle interfere with the vascular supply to the anterior segment. No formula establishes the number of muscles that can be safely detached, but once a muscle with its anterior ciliary arteries has been detached, the vessels cannot restore any perfusion to the anterior segment. As reported [4], a general rule is not to detach more than two rectus muscles at one time, unless absolutely necessary. For this reason, 6 muscles approach for EIE (involving MR, LR and IO, superior and inferior recti are not involved) does not represent a risk factor for anterior segment ischemia, in fact no anterior segment ischemia was reported. Refractive status was evaluated at last follow up. SE in RE ranged from -2.50 D to +5.75 D and in LE from -1.00 to +6.25 D, emmetropization was reported in 54 eye and myopic SE in 21 eyes. Hyperopic SE ≤ +1.50 D was reported in 48 eyes, > +1.75 < +3.25 D in 57 eyes and ≥3.50 D in 36 eyes.

Table 2 Deviation angle during follow-up *n* (%)

Follow-up	Ocular alignment (PD)				
	>-10	-1 to -10	0	+1 to +10	>+10
3mo	27 (25.0)	12 (11.1)	24 (22.2)	24 (22.2)	21 (19.4)
2a	12 (11.1)	24 (22.2)	18 (16.7)	24 (22.2)	30 (27.8)
5a	9 (8.3)	24 (22.2)	27 (25.0)	24 (22.2)	24 (22.2)
10a	12 (11.1)	24 (22.2)	30 (27.8)	27 (25.0)	15 (13.9)

Table 3 Horizontal deviation angle during follow-up in the two groups

Horizontal deviation angle (PD)	Before surgery	Follow-up			
		3mo	2a	5a	10a
≤40					
$\bar{x}\pm s$	37.50±4.2	-1.17±13.83	2.22±10.68	1.67±10.41	0.22±11.67
Range (min, max)	30, 40	-20, 30	-14, 30	-20, 20	-20, 30
Median	40	-2	0	0	0
>40					
$\bar{x}\pm s$	51.94±5.61	1.33±12.35	4.89±13.12	3.89±12.30	2.17±10.32
Range (min, max)	45, 60	-25, 25	-14, 30	-20, 20	-20, 18
Median	50	2	6	8	0

Table 4 Vertical deviation angle during follow-up in the two groups *n* (%)

Vertical deviation angle (PD)	Before surgery	Follow-up			
		3mo	2a	5a	10a
<8	6 (100)	36 (63.2)	27 (60)	36 (92.3)	21 (77.8)
≥8	0 (0)	21 (36.8)	18 (40)	3 (7.7)	6 (22.2)

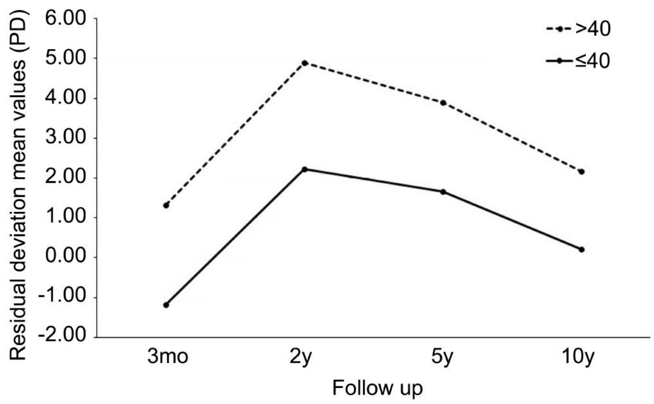

Figure 4 Residual deviation during follow-up in small and large angle esotropia group (≤40 PD and >40 PD).

Figure 5 shows the significant correlation between refractive error and 3mo residual deviation.

No significant correlation was found when refractive error and 10y residual deviation follow up were plotted. Myopic group sample size was inadequate to perform any comparison. Nevertheless, considering the significance of results, higher hyperopia and/or accomodative factors appear to have an important role in motor outcome. Before surgery BCVA at distance was recorded in 9 patinets (18 eyes: RE ranged from 0.22-0.04 logMAR; LE ranged from 0.40-0.04 logMAR).

After surgery BCVA at distance was recorded in 75 children (150 eyes; both RE and LE ranged from 0.30 to -0.14 logMAR). BCVA ranged from 0.3 logMAR to 0.2 logMAR in 36 eyes (21 RE, 15 LE); from 0.1 logMAR to 0 logMAR in 36 eyes (12 RE, 24 LE) and ≥0 logMAR in 78 eyes (42 RE, 36 LE).

Fifty-four patients performed occlusion treatment. Sensorial status was evaluated before surgery only in 3 patients who showed exclusion of one eye. After surgery, 9 patients showed alternating exclusion, 15 RE and 15 LE exclusion and 41 patients showed different level of BSV. Sensorial status was not recordable, after surgery, in 28 subjects. No complications such as scleral perforation or postoperative infections were recorded.

DISCUSSION

Different approaches for EIE management have been suggested by prospective, randomized multicenter trials over the last 20y, in order to define the best surgical timing and procedure [5]. Surgical timing issue is strongly controversial. Although surgery performed before 2 years of age might potentially improve binocular vision, it might also increase the risk of amblyopia, I O hyperfunction and LR pseudoparalyis.

On the other hand, although surgery performed later than 2 years of age allows to achieve an easier amblyopia management and more reliable evaluation, it might reduce the potential for the binocular vision development; squint mechanical component due to muscles contracture is also reported when "late" surgery was performed [6]. An higher prevalence of fusion and stereopsis after "early" treatment of EIE were recently reported [7]. Nevertheless the early surgery presents some risk.

In 2005, the early *vs* late infantile strabismus surgery study (ELISSS) reported better "gross" stereopsis at 6 years of age in chidren who underwent early surgery when compared to whom underwent "late" one [8]; no significant differences of deviation angle was described. In 2010, ELISSS published further results showing that the benefits of early surgery for gross binocular vision, were balanced by a higher re-operation rate [9]. Early surgery may also promote the development of cortical visual motion processing[10].

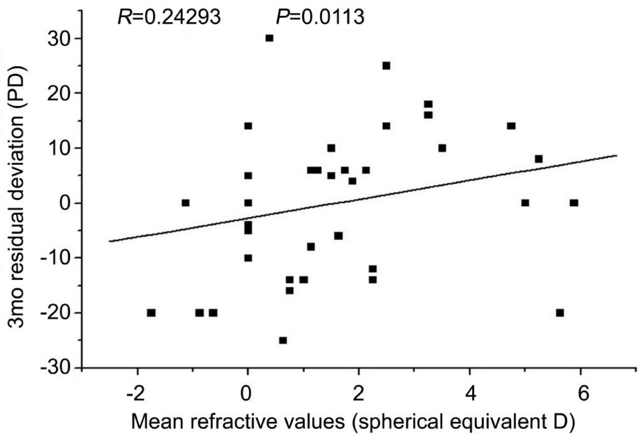

Figure 5 Correlation between 3mo residual deviation (PD) and spherical equivalent (D).

Although EIE treatment is centered on surgery, approach with the botulinum toxin (BT) has been described. Gursoy *et al*[11] reported no difference in ocular alignment when BT and surgical treatment were compared. By contrast, single-center, prospective, nonrandomized comparative study [12] suggested that surgery was more successful than BT in the treatment of large-angle esotropia. The study reported that BT was usefully treatment only for small- and moderate-angle infantile esotropia. BT has also been used in addition to surgery: Lueder *et al* [13-14] suggested, especially in large angle deviations, that augmentation with BT may be more effective than bimedial recessions alone. According to Elliott and Shafiq [6] review, surgical approach to EIE is debatable and multiple surgical techniques are currently used[5].

Whereas bilateral MR recession (BMR) technique is still suggested by some authors [15-16], non-significant differences were found when BMR and unilateral recession-resection technique were compared[17]. Helveston *et al*[18] successfully performed 8.0 to 10.0 mm BMR in 4mo children affected by IE, but long-term ocular alignment results were not ensured.

High success rate was related to three muscles approach (BMR associated with unilateral LR resection) [15-16,19-22]. Alternative 3 muscles approach were proposed considering LR plication[23] or Y-splitting.

Badawi and Hezagy[24] studied the effects of Y-split recession and BMR in patients affected by large angle infantile esotropia (IE), their result showed that Y-splitting technique was more difficult and time consuming than BMR, but both procedures were effective for the correction of <70 PD horizontal deviation. According to previous study [25], 2 muscles approach to small angle EIE was raccomanded, multiple muscles approach to large angle EIE achieved better motor outcome. Data from other our not yet published study showed that 6 muscles approach achieves better sensory outcome than 3 muscles one. Literature shows no sufficient evidences to state which technique should be considered better than others.

Considering our previous data and satisfactory long-term outcome, we chose to further study the 6 muscles approach. Our result, after mean follow up of 10y, showed 27.8% of orthotropic patients and 47.2% patients with a residual deviation ranging from -10 PD to +10 PD. The difference between data at 3mo and 10y after surgery underline the importance of a long-term follow up.

Sample size, detailed, standardized postoperative sensorial evaluations, a single surgeon and the same orthoptic team represent the main strengths of our work. Nevertheless this study presents some limitation, underlining the retrospective design of our work. Uncomplete preoperative sensorial data as well as BCVA are reported, due to age and poor cooperation; the correlation between vertical deviation in primary position and IO recession/anteriorization should be further analyzed, longer follow-up might be requires to evaluate sensory outcome and reoperation rate in adult age.

Long-term follow up result suggest that the 6 muscles approach, performed before 4 years of age, represent a effective surgical treatment in patients affected by EIE with IO overaction and LR pseudoparalisys. Our results suggest that hyperfunctioning IO treatment should not be postponed.

To our knowledge there are no randomized trial evaluating different surgical approach to EIE, a multicenter trial would be useful to determine which procedure is more effective.

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