

# Acute Diplopia of Non-neurological/restrictive Etiology: a Retrospective Comparative Study.

**Gustavo Savino**

Policlinico Gemelli Dipartimento di Invecchiamento Neuroscienze e Ortopedia

**Alessandra Scampoli** (✉ [alesscampoli@gmail.com](mailto:alesscampoli@gmail.com))

Policlinico Gemelli Dipartimento di Invecchiamento Neuroscienze e Ortopedia <https://orcid.org/0000-0002-9250-6994>

**Fabrizio Piccinni**

Policlinico Gemelli Dipartimento di Invecchiamento Neuroscienze e Ortopedia

**Roberta Mattei**

Policlinico A Gemelli: Policlinico Universitario Agostino Gemelli

**Annabella Salerno**

Policlinico Gemelli Dipartimento di Invecchiamento Neuroscienze e Ortopedia

**Emanuele Crincoli**

Policlinico Gemelli Dipartimento di Invecchiamento Neuroscienze e Ortopedia

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## Research Article

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# Abstract

## Purpose

To describe and compare the clinical features and management of different types of acute diplopia of non-neurological/restrictive etiology.

## Methods

Retrospective comparative study carried out reviewing medical records of forty-eight patients referred to one tertiary referral center between January 2016 and June 2020.

Thirty-two were classified as Acute Acquired Comitant Esotropia (AACE), 3 cases as type I (group A), 12 cases as type II (group B) and 17 cases as type III (group C). Four cases were classified as Decompensated MonoFixation Syndrome (DMFS) (group D), 6 cases as High Myopia-Comitant Esotropia (HMCE) (group E) and 6 cases as Sagging Eye Syndrome (SES) (group F). Patients with diplopia of neurological or restrictive etiology were excluded.

All patients underwent a complete orthoptic and ophthalmologic assessment with a postoperative follow-up of  $11.4 \pm 4.1$  months (ranging from 5 to 20 months).

## Results

Type 3 AACE (Group C) was the most frequent cause of diplopia among the groups (35.4%). High Myopia-Comitant Esotropia (Group E) and Sagging Eye Syndrome (Group F) were significantly older at onset and baseline examination (both  $P = .001$ ). Constant acute onset was significantly more represented in Group C ( $P = .026$ ) while all patients in Group F showed an intermittent onset. Near angle of deviation was significantly lower in Group E and Group F compared to Group C ( $P = .030$ ). A significantly higher near divergence fusion amplitude was detected in Group C ( $P = .017$ ). Compensation (angle of deviation increasing) at Prism Adaptation Test (PAT) was observed in 75% of total study population, without significant differences among group. Fifty-four % of the total sample underwent surgery as first or secondary treatment choice with good functional results regardless of pathogenesis.

## Conclusion

Demographic characteristics and clinical features (refraction, type of diplopia at onset, angle deviation, fusion amplitudes, response to prismatic correction) can differentiate different types of acute or subacute onset diplopia of not neurological/restrictive etiology.

## Introduction

Diplopia is a disabling symptom which may be the presenting feature of a large variety of ocular and neurological conditions.<sup>(1)</sup> It occurs in patients with normal and, more rarely, sub-normal, binocular

correspondence manifesting strabismus after visual system development.<sup>(2)</sup>

Acute, constant or inconstant, diplopia accounts for 0.1% of the patients that present at an emergency department. The underlying causes often range from central to peripheral microvascular, neurological or infiltrative diseases, although the reported frequencies vary greatly from study to study and in a variable reported rate the diplopia is of “undetermined etiology”.<sup>(1)</sup> In fact a constant or inconstant acute diplopia, in absence of clear ductions limitations, in some cases can be a consequence of sensory-motor system disfunction and/or of extraocular muscles and fascial system alterations. With different age groups distribution Acute Acquired Comitant Esotropia (AACE), Decompensated Monofixation Syndrome (DMFS), Sagging eye syndrome (SES) and High Myopia Comitant Esotropia (HMCE), can be cause of acute, constant or inconstant, diplopia.

The authors, hereby, describe and compare the demographics, clinical data, management and outcomes of different types of acute or subacute onset diplopia of not neurological/restrictive etiology in a single referred tertiary center (Ophthalmology Unit of the “Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome)

## Materials And Methods

The retrospective comparative study was approved by the Institutional Review Board (Head and Neck Department of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome) and was carried out following the principles outlined in the Declaration of Helsinki. Written informed consent was previously obtained from the recruited patients or their parents.

Patients with a diagnosis of type I-Swan (Group A), type II-Burian-Franceschetti (Group B) and type III-Bielschowsky (Group C) AACE, DMFS (Group D), HMCE (Group E), and SES (Group F) were enrolled.

HMCE Group included patients that were excluded from the Group C because of high myopic values, (> -8.00 spherical equivalent-SE), and that cannot also be classified as Heavy Eye Strabismus Fixus Syndrome due to the normal ductions and absence of ocular motility restrictions.

All patients were enrolled by retrospectively reviewing the medical records of patients referred to the Orthoptics and Pediatric Ophthalmology Department of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome between January 2016 and June 2020.

For each patient, the diagnosis was first suspected on the basis of their clinical history, presentation and imaging and then confirmed by examining their post treatments functional outcomes.

The exclusion criteria were, for all groups, a visual acuity less than 20/32 in the worst eye, Central Nervous System (CNS) diseases, Duane, Brown and alphabetic syndromes and the inability to cooperate with the administered tests (patients with an onset of strabismus before 4 years of age were excluded because of the inability to perform a complete clinical evaluation).

All patients underwent brain and orbital computed tomography and/or magnetic resonance imaging and to a neurological examination to rule out neurological diseases.

All patients underwent a complete orthoptic and ophthalmological assessment including best-corrected visual acuity (BCVA) measurement, near (33 cm) and far (6 meters) prism and alternating cover test (PACT) and ocular motility evaluation. The prismatic adaptation test (PAT) was performed by wearing prisms in the outpatient clinic, and the progressive prism test (PPT) by a Fresnel press-on prism application in the cases that “eat” the prisms applied. The target angle was the total deviation reached after the PAT Test and, in patients whose angle increased, after the PPT Test. In each patient, the final angle measured (target angle) and the compensation were repeated twice. Divergence and convergence fusional amplitudes (FA) were measured at distance and at near fixation through the full optical correction. An accommodative target was used first at distance (6 m) and then at near (33 cm). Starting from the base-out prisms totally compensating the deviation, base-out prisms of decreasing power and of increasing power were used to measure divergence and convergence FA, respectively. When two consecutive measurements gave the same result, this data was kept as valid. Before orthoptic assessment, cycloplegic refraction testing and fundus examinations were performed in all patients. All of the surgical procedures were performed in our clinic by two experienced surgeons (GS and AS) on the basis of the target angle: to correct higher angle values supramaximal recti recession was performed.

## Statistical analysis

Statistical analysis was conducted using SPSS software (IBM SPSS Statistics 26.0). Normality of the distribution for quantitative variables was evaluated using Shapiro-Wilk test. Normally distributed variables were described using mean and standard deviation while variables whose distribution differed from normality were described using median and interquartile range. Qualitative variables were described as number of cases over total and percentage. Inferential analysis of quantitative variables was preliminary performed using X<sup>2</sup> test or Fisher’s exact test and subsequent Bonferroni post-hoc test. Differences in quantitative variables between the groups were detected using a two way ANOVA with Bonferroni post hoc analysis. Lastly, variables that proved to be significant or nearly significant in the preliminary analysis were further evaluated by multinomial logistic regression. A p value < 0.05 was considered as statistically significant.

## Results

The study population included 48 caucasian patients with a mean age of  $39.71 \pm 20.4$  years. Male patients represented 56.2% of the cohort. Onset of diplopia occurred at a mean age of  $34.34 \pm 19.5$  years (Fig. 1) and it was of acute and constant onset in 14 patients (29.2%) and of inconstant onset in 34 patients (70.8%) (Fig. 2). Type 3 AACE ( Group C) was the most frequent cause of diplopia among the groups (17 patients, 35.4%), followed by type II AACE ( Group B) (12 patients, 25%), HMCE ( Group E) (6 patients, 12.5%) and SES ( Group F) (6 patients, 12.5%). Only 4 patients (8.3%) were diagnosed with DMFS ( Group D) and 3 patients (6.3%) with type I AACE ( Group A). The last two groups (group D and

group A) didn't take part in inferential analysis due to the small sample size and need for non-parametric tests for quantitative variables. Group E and Group F were significantly older at onset and baseline examination (both  $P = .001$ ) and more frequent in male sex ( $P = .049$ ) compared to Groups B and Group C.

Constant acute onset was significantly more represented in Group C compared to the other 3 Groups considered for analysis ( $P = .026$ ). In addition, all patients of Group A presented acute constant onset while all patients of Groups F and D developed the condition with an intermittent/inconstant pattern. Group B was the only group whose patients didn't show a myopic spherical equivalent ( $P = .001$ ). Detailed descriptive data are reported in Table 1.

Overall, the majority of patients reported both on near and distance fixation diplopia at diagnosis (66.7%) and only 2 patients showed at near diplopia only. Simultaneous at distance and at near diplopia compared to diplopia only at distance was instead more prevalent in the Group F compared to the others ( $P = .042$ ). Mean angle of deviation in the total population was  $24.5 \pm 12.2$  on distance fixation and  $22.02 \pm 13.25$  on near fixation. Near angle of deviation was significantly lower in Group E and Group F compared to Group C ( $P = .030$ ) (Fig. 3).

A significantly higher near divergence FA was detected in Group C ( $P = .017$ ) (Table 2).

Compensation (angle of deviation increasing) at PAT Test was observed in 75% of total study population, with a particularly high rate in Groups A, B, and E. Nevertheless, no significant differences among groups in terms of both rate of angle of deviation increasing and target angle, after PPT test, were observed. Moreover the difference between basal and target angle of deviation was not statistically significantly different among groups. At the end of PPT Test and wearing prisms the 66.7% of total sample showed no residual esodeviation and diplopia, the 25% presented esophoria with no diplopia. An esophoria was significantly more frequently observed in Group B ( $P = .002$ ) (Fig. 4).

Four cases, at the end of PPT, showed persistent esodeviation and diplopia despite the high value of prisms applied. The response was significantly more frequently observed in Group F ( $P = .040$ ). Twenty-six patients (54.2%) underwent surgery as first or secondary treatment choice but no diagnosis represented a preferred indication for surgery. At postoperative follow up (mean  $11.4 \pm 4.1$  months, ranging from 5 to 20 months) 46.2% of the patients showed esophoric horizontal deviation without diplopia and the 53.8% absence of diplopia and angle deviation with no differences between the groups.

## Discussion

Even if several ocular motility disorders, (AACE, MFSD, HMCE, SES) can lead to diplopia in different age groups in absence of neurological or restrictive factors, the clinical symptoms are often similar and the pathogenesis is often uncertain. Among the different causes that have been suggested refractive errors, sensory and motor dysfunctions, anatomical features and tissue ageing were reported.

Acute acquired comitant esotropia (AACE) is an unusual form of strabismus, of unknown etiology, that occurs in older children or, less commonly, in adults.<sup>(3,4)</sup> It is clinically characterized by the acute onset of large-angle esotropia and diplopia with minimal refractive error. Occasionally, AACE may present as intermittent esotropia that becomes constant over time. Burian and Miller classified AACE in 3 categories, based on clinical features and apparent etiology: type 1 (Swan): acute-onset esotropia following occlusion (due to interruption of fusion in children without a significant hyperopic refractive error), type 2 (Burian-Franceschetti): acute onset of concomitant strabismus, often with diplopia, in patients with hyperopia without an accommodative component, type 3 (Bielschowsky): AACE in myopic patients (<5 diopters) with constant esodeviation and typically a larger angle for distance than for near.<sup>(5)</sup>

The type 3 is usually associated to mean values of myopia of -5/6 diopter-spheres and nearly normal ocular ductions, with at most minimal limitation of abduction<sup>(6)</sup>. Other reports showed a higher myopic range, with a case of 17.5 diopters spherical equivalent, but with a mean value of 4.4 SE, normal ocular motility, normal AC/A ratio and normal divergence motor fusion.<sup>(7)</sup>

For this reasons we included the patients with high myopic SE (> 8 SE) in a different group (Group E)

Monofixation Syndrome (MFS) is a horizontal strabismus characterized by a small angle of deviation (less than <8 prism diopters [PD]), good fusional vergence amplitude and central suppression of the non-fixating eye under binocular viewing conditions. It is frequently associated with anisometropia and amblyopia of the deviated eye and some degree of stereoscopic sensitivity.

The stability of MFS is controversial; Parks believed that MFS did not change, whereas Hunt, Keech, Siatkowski and Ing<sup>(8,9,10,11)</sup> described different group of patients that, although being stable for many years, eventually lost their binocularity. MFS may decompensate, more often between 1 and 5 years of age (but sometimes later in life, as described by Siatkowski), with the development of large-angle esotropia and sometimes diplopia requiring surgical treatment to restore the binocular status<sup>12</sup>

In 2009 Rutar and Demer described binocular diplopia in not myopic elderly patients caused by orbital pulleys degeneration, and this condition was called Sagging eye syndrome (SES). Elderly patients develop esotropia for distance viewing and a small-angle hypotropia with decreased supraduction but full abduction. Clinical features of SES are based on motility patterns and adnexal abnormalities (blepharoptosis, superior sulcus deformity, etc). The relative proportion of SES patients among all diplopic patients was reported increasing with age up to 60.9% over the age of 90.<sup>(13)</sup>

To the best of the authors' knowledge, this study is the first to report and compare clinical features of constant or inconstant acute onset diplopia, of not neurologic/restrictive pathogenesis, in a large cohort of patients.

In our sample type 3 AACE and type 2 AACE were the most frequent cause of diplopia among the groups, 35.4% and 25% respectively.

Most of the patients from our study presented with intermittent inconstant onset, even if acute constant onset was particularly represented in Group C and Group A.

Age of onset was significantly higher in Group E and Group F compared to the other groups according to other reports.<sup>(13,14)</sup> Both were also more prevalent in male sex. This significantly differed from the other causes, affecting males and females regardless of gender. Other authors reported instead a female prevalence in high myopic diplopia<sup>(14)</sup> and SES<sup>(15)</sup>.

The near angle of deviation was significantly lower in Groups E and F, this, together with the higher age of onset can suggest a similar pathogenesis. In fact both SES and HMCE show Magnetic Resonance Imaging degeneration of the superior-lateral rectus band with a consequent lateral rectus inferiorly dislocation.<sup>(13)</sup> The classic Heavy Eye Syndrome, HES, or strabismus fixus shares the same pathogenesis, a nasal displacement of the superior rectus muscle and an inferior displacement of the lateral rectus muscle, but with a superotemporal quadrant posterior globe prolapse<sup>(16,17,18,19)</sup>

The pathogenesis of diplopia in Group C remains uncertain but it seems to be different from the assumed anatomical cause of Groups E and F. Patient of Group C showed a significantly higher incidence of acute constant diplopia onset and a significantly higher near divergence FA, according to other reports<sup>(7)</sup>. Other Authors reported a higher accommodative convergence to accommodation ratio (AC/A) in these patients<sup>(20)</sup>

A large proportion of the whole sample showed angle increasing at PAT test, 75% of the total sample, with no significant differences between different groups. In addition no significant difference was found in term of target angle and rate of angle increasing among groups. In a previous study it was reported that, also in the presence of normal retinal correspondence, an unexpected overcompensating prism response could be observed.<sup>(12)</sup> This phenomenon was found to be similar to the PAT results in ARC.<sup>(21)</sup> Therefore, both patients with anomalous and normal retinal correspondence may respond to the PAT overcompensating. The cause of the high percentage of patients who had building-up of angle with prisms isn't currently well understood; we can suppose that a long standing convergent position together with rooted anomalous convergent movements would increase the medial recti tonus. The good functional response, regardless of pathogenesis, also for the patients that showed diplopia at PPT Test, to the surgical treatment planned based on the target angle and not on the basal angle measured under casual viewing, confirmed, according to previous reports,<sup>(12,15)</sup> that this is an actual and not prism-induced phenomenon.

In conclusion, age of onset of diplopia, gender, presenting clinical features (constant/inconstant diplopia-distance/near diplopia), refraction, response to PPT Test can allow/support for the differentiation between several types of ocular motility disorders and diplopia of not neurological/restrictive etiology and lead to a personalized functional prognosis as well as to an appropriate surgical treatment plan. Further prospective multicenter studies are warranted to better define the clinical features and the

pathogenesis of such heterogeneous and often life-limiting diseases to move toward a tailored therapeutic approach.

## Declarations

### Funding

The authors did not receive support from any organization for the submitted work.

### Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

### Availability of data and material

Available

### Authors' contribution

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

### Code availability

Not applicable

### Ethics approval and consent to participate

The retrospective comparative study was approved by the Institutional Review Board (Head and Neck Department of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome) and was carried out following the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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## Tables

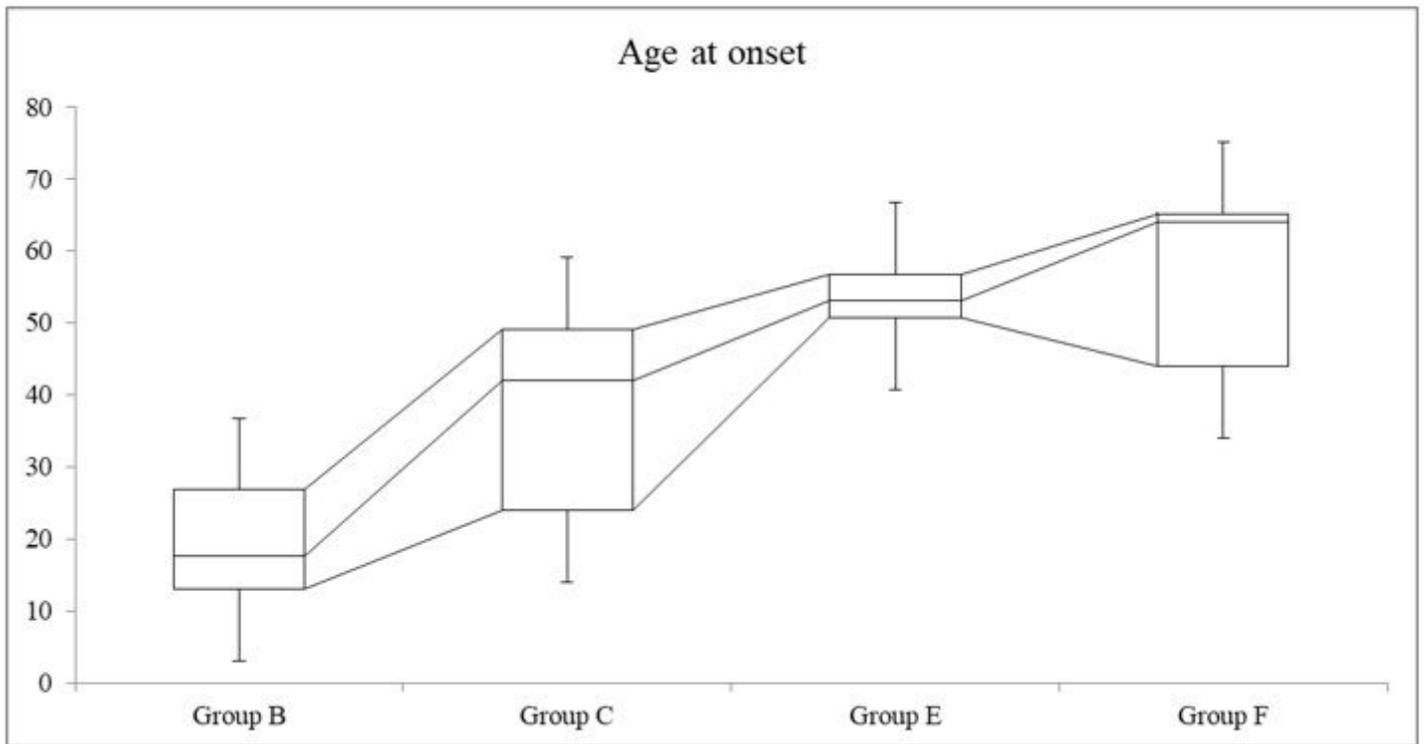
**Table 1.** Clinical characteristics at presentation of total population and subgroups. SE: Spherical Equivalent; LE: left eye; RE: right eye, M: male F: female \*= these groups didn't take part in inferential analysis; Group A: AACE type I; Group B: AACE type II; Group C: AACE type III; Group D: DMFS; Group E: HMCE; Group F: SES.

		Total sample	Group B	Group C	Group E	Group F	Group D *	Group A*	P
<b>N of patients</b>		48	12/48 (25%)	17/48 (35.4%)	6/48 (12.5%)	6/48 (12.5%)	4/48 (8.3%)	3/48 (6.3%)	
<b>Gender</b>	<b>M</b>	27/48 (56.2%)	5/12 (41.7%)	9/17 (52.9%)	5/6 (83.3%)	5/6 (83.3%)	2/4 (50%)	1/3 (33.3%)	<b>0.049</b>
	<b>F</b>	21/48 (43.8%)	7/12 (58.3%)	8/17 (47.1%)	1/6 (16.7%)	1/6 (16.7%)	2/4 (50%)	2/3 (66.7%)	
<b>Age of onset</b>		34.34 ± 19.5	20.6 ± 16.0	36.3 ± 13.9	58.3 ± 5.5	55.4 ± 15.3	14 (10)	11 (1)	<b>0.001</b>
<b>Type of onset</b>	<b>Constant</b>	14/48(29.2%)	2/12(16.7%)	8/17(47.1%)	1/6(16.7%)	0/6 (0%)	0/4 (0%)	3/3(100%)	<b>0.026</b>
	<b>Inconstant</b>	34/48(70.8%)	10/12(83.4%)	9/17(52.9%)	5/6(83.3%)	6/6 (100%)	4/4(100%)	0/3(0%)	
<b>SE (RE)</b>		-3.53 ± 6.1	+0.25 ± 1.1	-4.7 ± 2.4	-12.7 ± 5.2	-3.6 ± 4.7	0.30 (0.75)	5 (3.25)	<b>0.001</b>
<b>SE (LE)</b>		-3.3 ± 5.5	-0.37 ± 2.17	-4.6 ± 2.4	-13.0 ± 9.6	-3.1 ± 4.8	0.30 (0.75)	2 (0.5)	<b>0.001</b>
<b>Diplopia</b>	<b>For distance</b>	14/48 (29.1%)	2/12 (16.7%)	7/17 (41.2%)	2/6 (33.3%)	1/6 (16.7%)	1/4(25%)	1/3 (33.3%)	<b>0.056</b>
	<b>For Near</b>	2/48 (4.2%)	1/12 (8.3%)	0 (0%)	0 (0%)	0/6 (0%)	1/4(25%)	0/3(0%)	<b>0.96</b>
	<b>For distance and near</b>	32/48 (66.7%)	9/12 (75%)	10/17 (58.8%)	4/6 (66.6%)	5/6 (83.3%)	2/4(50%)	2/3(66.7%)	<b>0.042</b>

**Table 2.** Angle deviation, FAs, PAT and PPT tests responses and treatment outcomes for total population and subgroups. FA = Fusion amplitude; PAT = Prismatic Adaptation Test; PTT =Progressive Prism Test \*= these groups didn't take part in inferential analysis; Group A: AACE type I; Group B: AACE type II; Group C: AACE type III; Group D: DMFS; Group E: HMCE; Group F: SES.

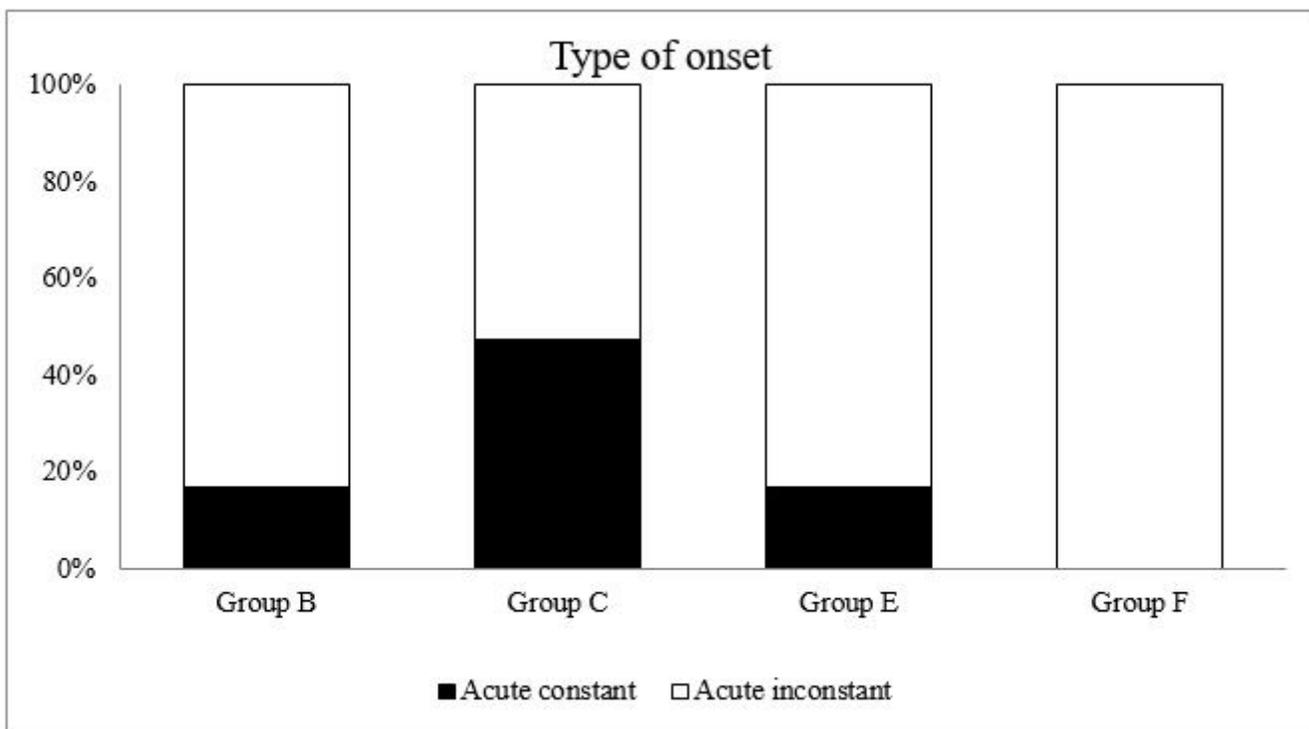
		Total sample	Group B	Group C	Group E	Group F	Group D*	Group A*	P
Angle of deviation (at distance)		24.5 ± 12.2	24.5 ± 9.1	29.2 ± 10.7	19.0 ± 13.9	16.0 ± 13.6	30(0)	45(24.5)	0.37
Angle of deviation (at near)		22.02 ± 13.25	20.3 ± 3.7	23.6 ± 4.3	14.0 ± 6.2	14.2 ± 5.8	37.5 (5)	45(12.5)	<b>0.030</b>
FA	Covergence (at distance)	14.8 ± 6.5	15.7 ± 1.9	16.7 ± 2.1	15.3 ± 6.4	12.0 ± 4.9	13(3)	14(4)	0.19
	Convergence (at near)	21.1 ± 9.1	25.1 ± 9.3	22.6 ± 7.2	18.3 ± 7.6	15.4 ± 6.1	22.5(1.25)	18(2)	0.142
	Divergence (distance)	3.1 ± 2.9	2.6 ± 1.1	4.7 ± 2.4	2.67 ± 1.1	2.4 ± 0.9	8(0)	5(1)	0.153
	Divergence (near)	5.6 ± 4.5	6.2 ± 2.5	9.3 ± 2.2	4.0 ± 2.2	2.4 ± 0.9	5(1)	7(1)	<b>0.017</b>
Patients whose angle increased at PAT Test		36/48 (75%)	10/12 (83.3%)	10/17 (58.8%)	6/6 (100%)	5/6 (83.3%)	2/4 (50%)	3/3 (100%)	0.14
Difference between basal and target angle		5.9 ± 14.4	8.6 ± 17.2	3.2 ± 16.7	4.8 ± 8.7	0.3 ± 0.8	16.2 ± 12.5	11.7 ± 11.5	0.47
Response to PAT and PTT Test	Absence of diplopia and angle deviation	32/48 (66.7%)	7/12 (58.3%)	13/17 (76.5%)	5/6 (83.3%)	4/6 (66.6%)	1/4 (25%)	2/3 (66.7%)	0.12
	Esophoria without diplopia	12/48 (25%)	4/12 (33.3%)	3/17 (17.6%)	1/6 (16.7%)	1/6 (16.7%)	3/4 (75%)	0/3 (0%)	<b>0.002</b>
	Esotropia and diplopia	4/48 (8.3%)	1/12 (8.3%)	1/17 (5.9%)	0/6 (0%)	1/6 (16.7%)	0/4 (0%)	1/3 (33.3%)	<b>0.040</b>
Surgical treatment		26/48 (54.2%)	9/12 (75%)	10/17 (58.8%)	2/6 (33.3%)	2/6 (33.3%)	2/4 (50%)	1/3(33.3%)	0.21
Response to surgical treatment	Esophoria without diplopia	12/26 (46.2%)	4/9 (44.4%)	5/10 (50%)	1/2 (50%)	0/2 (0%)	2/2(100%)	0/1 (0%)	0.72
	Absence of diplopia and angle deviation	14/26 (53.8%)	5/9 (55.6%)	5/10 (50%)	1/2 (50%)	2/2 (100%)	0/2 (0%)	1/1 (100%)	0.56

## Figures



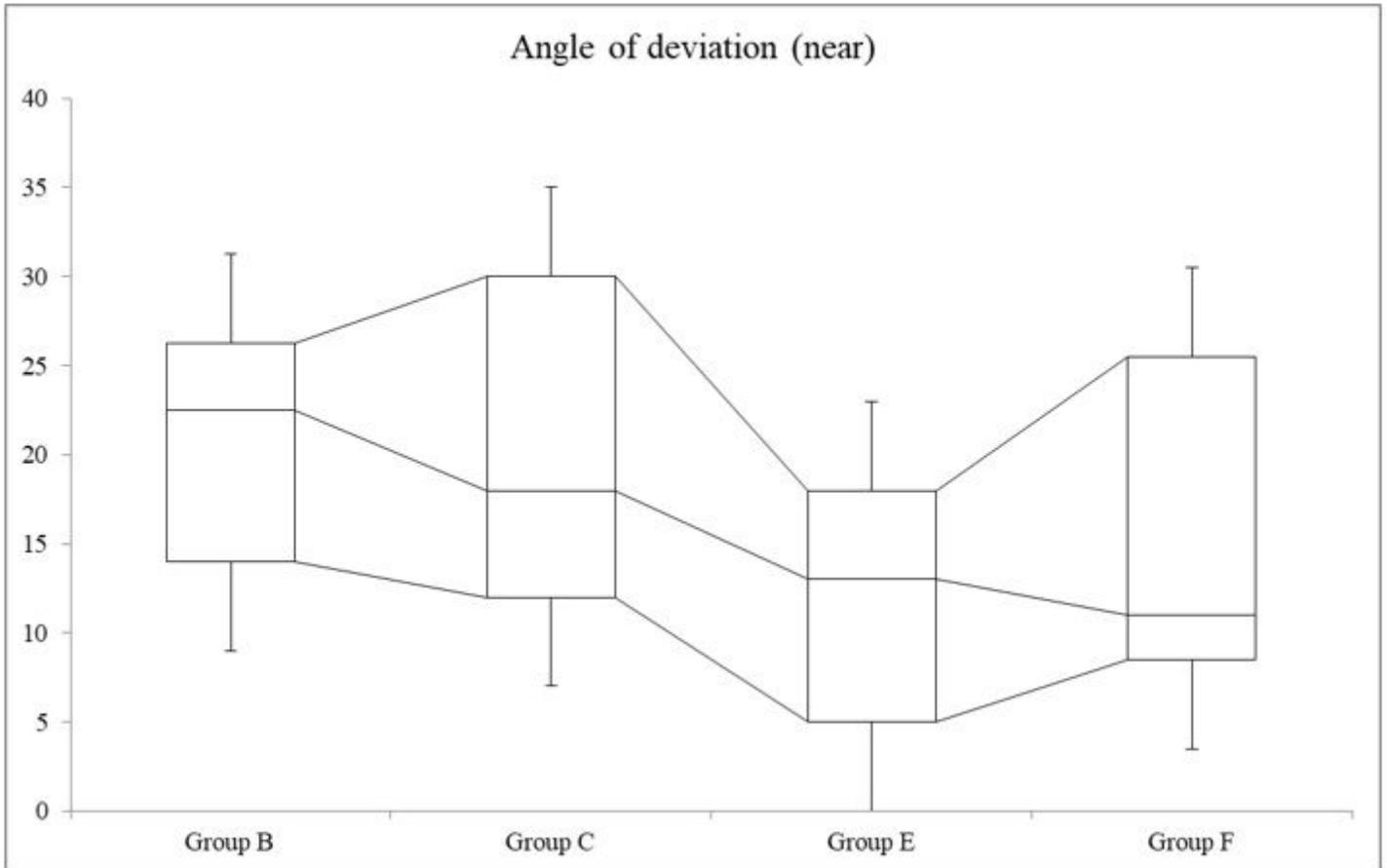
**Figure 1**

Box plot showing distribution of age at onset in the study groups; Group B: AACE type II; Group C: AACE type III; Group E: HMCE; Group F: SES.



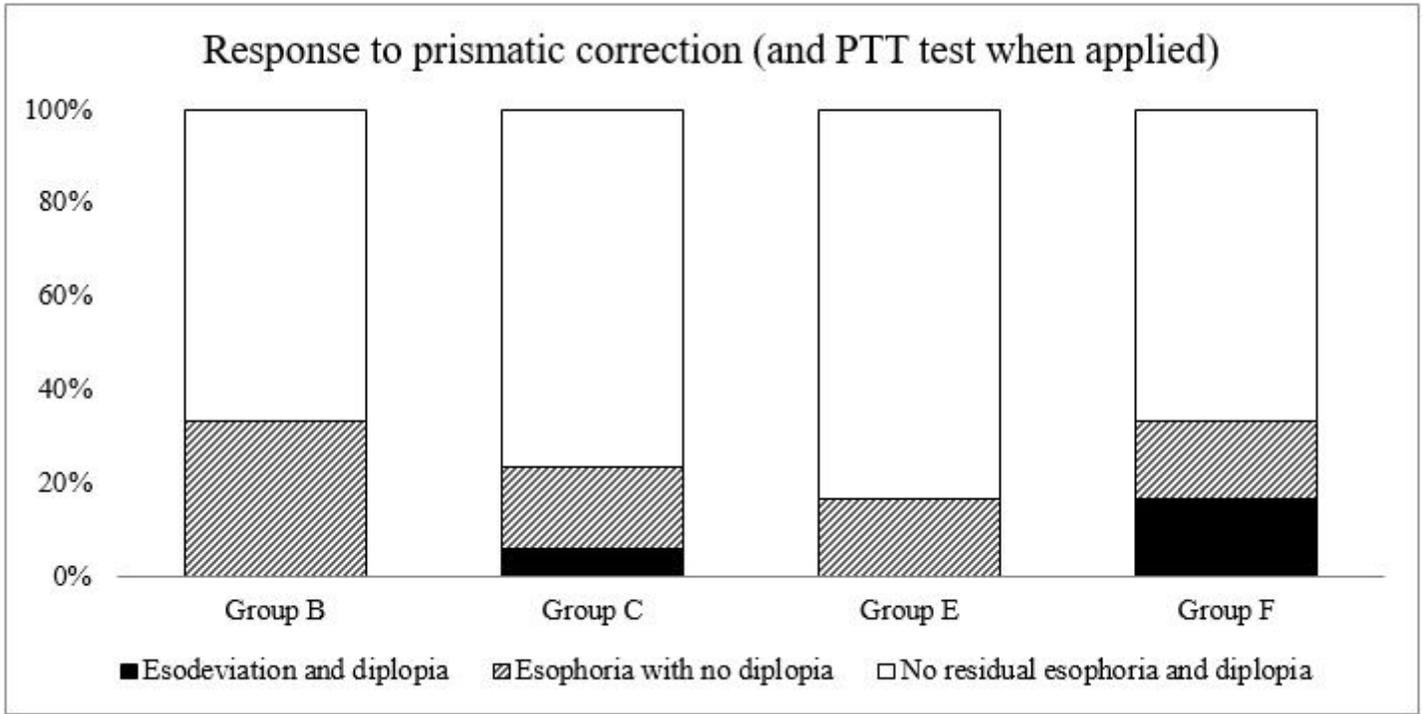
**Figure 2**

Percentage distribution of type of onset (Constant/Inconstant) in the study groups. Group B: AACE type II; Group C: AACE type III; Group E: HMCE; Group F: SES.



**Figure 3**

Box plot showing distribution of angle of deviation at near in the study groups; Group B: AACE type II; Group C: AACE type III; Group E: HMCE; Group F: SES.



**Figure 4**

Percentage distribution of type of response to prismatic correction in the study groups; Group B: AACE type II; Group C: AACE type III; Group E: HMCE; Group F: SES.