Independent risk factors of type III acute acquired concomitant esotropia: A matched case–control study

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Purpose: To investigate the risk factors and surgical design for type III acute acquired concomitant esotropia (AACE). Methods: In this retrospective, matched, case–control study, 51 patients developed type III AACE between March 2018 and September 2020, and the control group consisted of 60 patients matched by age and refractive power during the same period. A history of the duration of near work per day and the use of glasses were reviewed, and the refractive power of both eyes, deviation angles at both near and far vision, visual function, and treatment options were analyzed. Additionally, the distance from medial rectus insertion to the limbus was measured in surgical patients. The data were analyzed by logistic regression analysis. Results: We found that 99.96% of the patients and 91.67% of the controls had myopia. Of these, 60.8% and 20.0%, respectively, did not wear glasses for near work. Twelve patients were treated with a prism and 39 were treated surgically. The average time devoted to near work per day was 7.24 and 3.7 h by the patients and controls, respectively. Univariate logistic regression analysis showed that increased hours of near work per day and near work without the use of spectacles were associated with the incidence of type III AACE. Multiple logistic regression analysis revealed that increased hours of near work per day and near work without the use of glasses were independent risk factors for AACE. Conclusion: Increased hours of near work per day and uncorrected myopia in near work are independent risk factors for type III AACE.

Key words: Acute Acquired Concomitant Esotropia, case–control studies, logic models, myopia, risk factors

Acute acquired concomitant esotropia (AACE) is a relatively rare subtype of esotropia that can develop in older children (age >5 years), adults, and older adults.[1-3] In 1958, Burian and Miller[4] defined three main types of AACE: (1) type I AACE (Swan type) occurs due to the disruption of fusion precipitated by monocular occlusion or impaired vision in one eye; (2) type II AACE (Burian-Franceschetti type) is characterized by large deviation, mild hyperopia, and minimal accommodative element and can be associated with physical or mental stress; and (3) type III AACE (Bielschowsky type), which was first reported by Bielschowsky, with onset after adolescence in patients with myopia. It is characterized by unique clinical features such as a small initial esodeviation, which presents only at distance fixation. Diplopia appears at near vision with disease progression. The incidence of type III AACE has reached its highest with its dramatic increase during the coronavirus disease pandemic lockdown due to the increase in near work.[5] Type III AACE affects the vision and causes uncomfortable diplopia, significantly reducing quality of life and possibly damaging visual function.

The exact mechanism underlying this prevalent type of AACE is not fully understood. Several potential risk factors for type III AACE have been proposed, including fusion dysfunction and disruption, esophoria, myopia, and anatomical structures.[1,3-6,8] However, the role of uncorrected myopia as a risk factor for type III AACE remains controversial. Previous studies[6,10] proposed that an individual with uncorrected myopia tends to hold objects excessively close to the eyes, resulting in an imbalance between the converging and diverging forces of the eyes. In contrast, Ruatta et al.[12] did not consider type III AACE to originate from uncorrected myopia because the patients usually wore corrective glasses. The sample sizes of studies on risk factors that have been conducted until now have been relatively small, with most being case series reports. Thus, no evidence to explain this problem has been provided yet.

In this study, we designed a retrospective analysis of the clinical characteristics of patients with type III AACE who were matched by age and refractive power to controls. Multiple regression analysis was applied to explore the risk factors and the impact of the surgical design of the subtype on esotropia and gain insights into the pathogenesis. We present the following article in accordance with the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.
Methods

Study design and ethical approval

This retrospective matched case-control study conformed with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Fujian Medical University (IRB No. [2015] 084-1). Signed informed consent was obtained from the patients or their guardians.

Patient population

The medical records of 51 patients diagnosed with type III AACE from March 2018 to September 2020 at the ophthalmic center of the First Affiliated Hospital of Fujian Medical University were retrospectively reviewed. Type III AACE was diagnosed based on the presence of acute acquired concomitant nonaccommodative esotropia after 5 years of age and diplopia presenting at fixation distance initially, with deviation showing a difference within 5 prism diopters (PD) in all directions of gaze, without eye movement limitation. Patients with systemic diseases, such as hyperthyroidism and myasthenia gravis, which may cause diplopia, or a history of head injury, neurological deficits, ophthalmic surgery, and strabismus during infancy were excluded. In the same period, another 60 outpatients without type III AACE diagnosis from the same ophthalmic center were selected as controls. Considering that refractive power (diopter [D]) was a crucial factor affecting the use of glasses by patients, the recruited participants were matched by age (±5 years) and refractive power (±1 D) to the AACE group in a 1:1 ratio. Individuals with diagnoses of ocular and systemic diseases other than ametropia were excluded from the control group. A history of the duration of near work (≤30 cm) per day, which included hours of work per day on a mobile phone, computer, and non-video display terminal (non-VDT), and the use of glasses, especially at near work, were carefully recorded for all participants. However, because this was a retrospective study, the dates of eye position before onset were imperfect and the hours of near work were imprecise, as they depended on patient recall.

Clinical tests

All participants underwent a cycloplegic refractive power assessment. Participants aged over 12 years were administered 0.5% tropicamide, while patients aged under 12 years were administered 1% atropine eye ointment. In the AACE group, the Hirschberg test was performed to assess the corneal light reflex, followed by the alternate prism cover test for all directions of gaze, both at near (33 cm) and distance fixation (6 m). The objective deviation of esotropia was evaluated using the prism and alternative cover test; the base-out prisms were gradually increased until exotropia occurred, and subsequently, the prisms were gradually decreased up to the power at which the eye did not move. Notably, significant findings were recorded in PD. The simultaneous perception was evaluated with Bagolini glasses. Fusion was assessed with synoptophore, and near stereopsis was assessed with the Titmus test.

Treatment

Prism correction was performed for patients whose deviation was ≤15 PD; the prisms were equally distributed to both eyes as far as possible. Surgery could be performed when deviation was >15 PD and following the stabilization of esotropia: a unilateral (non-dominant eye) or bilateral medial rectus muscle recession for deviation <40 PD, a unilateral medial rectus recession combined with lateral rectus resection for deviation ≥40 PD, or a bilateral medial rectus recession and unilateral lateral rectus resection for deviation >90 PD. Local infiltration anesthesia combined with surface anesthesia was administered. Simultaneously, intravenous injection of a small dose of sedative and analgesic drugs was administered by an anesthesiologist to keep patients who could not tolerate local anesthesia awake during the operation. The distance from the insertion of the medial rectus to the limbus was measured with
a caliper before the muscle was cut. Intraoperative adjustable sutures placed as a loose knot were tied on the muscle. The patients were seated with appropriate refractive glasses for near and distance targets.

A resolution of near and distant diplopia and esophoria of ≤8 PD after the treatment was defined as successful treatment. The follow-up period was at least 6 months, and the angle of deviation, diplopia, and visual function were measured at follow-up visits. The same senior physician provided the diagnosis, determined surgical design, and conducted follow-up for all participants.

Statistical analysis
Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The age and spherical equivalent (SE) between the AACE and control groups were compared by the Wilcoxon signed-rank test. The difference in the pre- and post-treatment angle of deviation and visual function was evaluated by Fisher’s exact test. The risk factors for type III AACE were analyzed by univariate and multivariate logistic regression models. *P* values of <0.05 were considered statistically significant.

Results
Baseline features
The AACE group included 51 patients, 35 men (66.7%) and 17 women (33.3%). The control group comprised 60 patients, that is, 31 males (51.7%) and 29 females (48.3%). The mean age of onset was 26.40 ± 8.67 (range: 10–51) years and 26.94 ± 10.41 (range: 11–56) years in the control and AACE groups, respectively [Fig. 1a]. Fifty-five (91.67%) patients presented with myopia, with a mean SE of −3.69 ± 1.82 (range: +1.25 to −6.50) D on the right eye and −3.64 ± 1.83 (range: +2.00 to −6.75) D on the left eye in the AACE group. Moreover, 49 (99.96%) patients presented with myopia, with a mean SE of −3.69 ± 1.82 (range: +1.25 to −6.50) D on the right eye and −3.64 ± 1.83 (range: +2.00 to −6.75) D on the left eye in the AACE group [Fig. 1b]. The differences in age and SE between the AACE and control groups were not significant (*P* > 0.05). Each participant showed a binocular corrected visual acuity of 20/20 on their first visit. The mean duration of near work per day was 3.7 ± 1.29 (range: 2–7) h and 7.24 ± 1.91 (range: 4–12) h in the control and AACE groups, respectively. The mean duration of diplopia was 22.85 ± 27.49 (range: 0.1–132) months, and diplopia, which although generally presented at distance fixation initially, was more evident at near fixation in the AACE group.

A comparison of clinical features between the AACE and control groups is provided in Table 1.

Treatment outcomes
In the AACE group, 12 patients were treated with prism correction and 39 were treated with surgery. The deviation angles at distance and near 6 months post-treatment in these two groups were significantly different compared with pretreatment angles (all *P* < 0.05), indicating the validity of the two treatment methods [Table 2]. Only one patient had long-term near work of more than 10 h per day after surgery, and the condition recurred 1 year later. The success rate of the surgery was 99.97%. As shown in Table 2, most patients presented with simultaneous perception before treatment. Additionally, the number of patients with three grades of binocular visual function 6 months post-treatment in the two groups was significantly higher than that before treatment (all *P* < 0.05). The mean distance between the insertion of the medial rectus and limbus was 4.68 ± 0.54 (range: 3–5.5) mm in the surgical patients.

Risk factors
Univariate logistic regression analysis showed that increased hours of near work per day and near work without glasses were individually associated with an increased risk of type III AACE (*P* < 0.05) [Table 3]. Multiple logistic regression analysis revealed that the increased hours of near work per day (*β* = 1.947, *P* < 0.001) and near work without glasses (*β* = 3.007, *P* < 0.05) were independent risk factors for AACE [Table 4]. Near work per day was ranked high in the comparison of the importance of risk factors, including age, sex, SE refraction, failure to wear glasses, and amount of near work per day, in the AACE group [Fig. 2].

Discussion
To the best of our knowledge, this is the first matched case–control study to report the risk factors for type III AACE.

### Table 1: Comparison of clinical factors between the control and AACE groups

|                        | Control group | AACE group | *P*  |
|------------------------|---------------|------------|------|
| ![AACE=acute acquired concomitant esotropia, OD=oculus dexter, OS=oculus sinister](https://example.com) | ![AACE=acute acquired concomitant esotropia, OD=oculus dexter, OS=oculus sinister](https://example.com) | ![AACE=acute acquired concomitant esotropia, OD=oculus dexter, OS=oculus sinister](https://example.com) | ![AACE=acute acquired concomitant esotropia, OD=oculus dexter, OS=oculus sinister](https://example.com) |
| Sex                     |               |            |      |
| Male                    | 17 (33.3%)    | 35 (66.7%) | 0.13 |
| Female                  | 29 (48.3%)    | 31 (57.9%) |      |
| Age (years)             | 10–51 (26.40±8.67) | 11–56 (26.94±10.41) | 0.91 |
| Spherical equivalent (D) | +2.50 to −6.50 (−3.06±1.99) | +1.25 to −6.50 (−3.69±1.82) |      |
| OD                      | +2.50 to −6.50 (−3.06±1.99) | +1.25 to −6.50 (−3.69±1.82) | 0.13 |
| OS                      | +1.50 to −7.00 (−3.15±2.01) | +2.00 to −6.75 (−3.64±1.83) | 0.18 |
| Myopia                  | 55 (91.67%)   | 49 (99.96%) |      |
| Close work per day (h)  | 2–7 (3.7±1.29) | 4–12 (7.24±1.91) |      |
| Not wearing glasses     | 40 (20.0%)    | 31 (60.8%) |      |
| Diplopia duration (months) | 0.1–132 (22.85±27.49) | 3–5.5 (4.68±0.54) |      |
| Distance from the medial rectus insertion to the limbus (mm) | 3–5.5 (4.68±0.54) |
### Table 2: Comparison of clinical factors between the pretreatment and posttreatment groups

|                     | Operation group (n=39) | Prism group (n=12) |
|---------------------|------------------------|--------------------|
|                     | Preoperation | Postoperation | Pretreatment | Posttreatment |
| Deviation angles    |                     |                   |              |              |
| Distant             | +20 to+115 (+46.54±24.66) | 0 to+8 (+3.42±2.93)* | +4 to+15 (10.08±3.80) | 0 to+4 (2±1.48) * |
| Near                | +20 to+110 (+42.69±25.13) | 0 to+5 (+1.85±2.17)* | +4 to+15 (7.67±4.12) | 0 to+2 (0.42±0.67)* |
| Visual function, n (%) |            |                   |              |              |
| Simultaneous perception | 34 (87.2) | 36 (92.3)* | 9 (75.0) | 11 (91.7)* |
| Fusion              | 15 (48.4) | 15 (48.4) | 5 (41.7) | 10 (83.3)* |
| Stereopsis          | 7 (17.9) | 23 (59.0)* | 3 (25.0) | 7 (58.3)* |

*versus P <0.05

### Table 3: Univariate logistic regression analysis for AACE risk factors

|                        | β   | Statistic | P       | OR (95% CI) |
|------------------------|-----|-----------|---------|-------------|
| Sex                    | 0.636 | 1.591      | 0.112   | 1.871 (0.865-4.047) |
| Age                    | 0.006 | 0.301      | 0.763   | 6.2 (2.660-14.452)  |
| Near work per day (h)  | 1.802 | 4.823      | <0.001  | 1.006 (0.967-1.047) |
| Not wearing glasses    | 1.824 | 4.225      | <0.001  | 6.062 (2.915-12.609) |
| Spherical equivalent (D) |       |           |         |             |
| OD                     | -0.177 | -1.703    | 0.099   | 0.838 (0.683-1.027)  |
| OS                     | -0.135 | -1.331    | 0.183   | 0.873 (0.716-1.066)  |

AACE=acute acquired concomitant esotropia, CI=confidence interval, OD=oculus dexter, OR=odds ratio, OS=oculus sinister

### Table 4: Multivariate logistic regression analysis of risk factors for AACE

|                                  | β   | Statistic | P       | OR (95% CI) |
|----------------------------------|-----|-----------|---------|-------------|
| Near work per day (h)            | 1.947 | 4.513      | <0.001  | 7.011 (3.01-16.33)     |
| Not wearing glasses              | 3.007 | 3.282      | 0.001   | 20.229 (3.359-121.835) |

AACE=acute acquired concomitant esotropia, CI=confidence interval, OR=odds ratio

Additionally, this experimental design includes the highest number of participants so far, whereas previous studies predominantly comprised case report series.

Type III AACE is an acquired esotropia that occurs after 5 years of age after the visual function has matured. In this study, all patients had the unique features associated with type III AACE, such as sudden-onset esotropia and horizontal ipsilateral diplopia, an equal angle of deviation in all gazes without ocular movement abnormality, and paralysis of the extraocular muscles. Intermittent diplopia only appeared at distance fixation initially. With the progression of the disease, diplopia manifests at near fixation, according to previous reports. The etiopathogenesis of this esotropia subtype is still debated; hence, the reason for the increase in its incidence is unclear. In normosensorial individuals, sufficient divergent fusional amplitude (FA) compensates for the esodeviation to avoid diplopia. On the contrary, diplopia may emerge as long as there are risk factors for decreased divergence ability. In this study, we suggest that increased hours of close work per day and uncorrected myopia in near work are independent risk factors for type III AACE according to logistic regression analysis.

Prolonged near work was ranked highest in the importance analysis. We suggest that excessive near work leads to persistent convergence and development of increased tonus of the medial rectus muscles, gradually evolving into spasticity, denaturation, and fibrosis and eventually creating a leash. Lee et al. reported that patients with AACE used a smartphone close up more than 4 h per day before onset, which resulted in abnormalities of convergence and accommodations. Zheng et al. showed that patients with type III AACE spent a longer time performing tasks requiring near vision, ranging from 6 to 13 h per day, before the onset of double vision, and pathological examination revealed the abundance of collagenous fibers caused by the lack of medial rectus muscle fibers in these patients. The medial rectus could not relax effectively, and the ability to diverge was more evidently decreased at distance fixation. Although the deviation in distance in our study tended to be larger, the angle at near and distance showed a difference within 5 PD. Diplopia developed once the divergent function could not compensate for esotropia. This may justify why diplopia mostly presents at distance fixation initially.

Multiple logistic regression analysis also revealed that uncorrected myopia in near work is an independent risk factor for type III AACE. Because of the strong collinearity between the SE and duration of close work per day, SE of myopia was not included in the multiple logistic regression model. Our study found that 99.96% of patients (49/51, 99.96%) were myopic, and approximately 60.8% (31/51) did not wear glasses while performing near work. These data indicate that uncorrected myopia in near work has a significant correlation with the incidence of AACE. Burian et al. proposed that in patients with uncorrected myopia who tend to hold prints close to the eyes excessively, compensatory fusional divergence would not be able to compensate for the increased tonus in the medial
rectus muscles, resulting in esotropia. In contrast, it is well known that not wearing myopic glasses for near work reduces the accommodative convergence and is more likely to cause exophoria. Other factors may promote the onset in patients with uncorrected myopia. Recently, Ali et al.\(^8\) suggested that patients present with decompensating esophoria before the onset of symptomatic diplopia. Esophoria slowly worsened, and esotropia subsequently manifested when the divergence FA of patients increased. Convergence relaxation of the eyes increases with decreasing fixation distance to overcome esophoria. Ordinarily, compared with uncorrected myopia, corrected myopia requires accommodative effort for near, which causes more convergence transferred to distance vision. The divergence ability of the eyes, which is necessary to overcome esophoria, is more exercised in corrected myopia. Under adverse conditions, such as excessive near work, esophoria would be more easily decompensated in uncorrected myopia.

In this study, the mean distance from the insertion of the medial rectus to the limbus was 4.68 ± 0.54 (range; 3–5.5) mm in patients who required surgery. Cai et al.\(^8\) also found that the distance from the location of the insertion to the limbus of the medial rectus was 4.8 ± 0.4 mm in AACE. We believe that since the insertion of the medial rectus in patients with type III AACE is more forward than that in healthy individuals, the tension of the medial rectus muscle increases at near fixation. Esotropia is more likely to develop because of the interrupted balance between convergence and divergence.

We observed large variability in the onset age in this study, with the youngest and oldest patients being 11 and 56 years old, respectively, similar to the study by Ruatta et al.\(^2\) In the study, young children and people beyond presbyopic age (>40 years) with the same clinical features were included in the analysis of risk factors for AACE, and the abovementioned pathogenic mechanisms were observed in these two special groups. It was assumed that AACE is caused by excessive accommodation leading to undue convergence. In this study, we found that this esotropia subtype may develop even in presbyopic patients in whom accommodation is descending. Ruatta et al.\(^2\) also showed that accommodative functions in these patients were normal, indicating that the single mechanism of accommodation cannot explain the causes of AACE. Prolonged near work leads to the inability of the medial rectus to relax effectively, and esophoria decompensation in uncorrected myopia may also be the main cause in presbyopic patients.

Recent studies have shown that neurological diseases rarely exist in patients with AACE; similarly, no patients with neurological disorders were observed in our study. AACE may be associated with neurological diseases. Based on this finding, some researchers believe that the etiology of AACE may not be related to the risk of intracranial lesions. However, delayed esotropia remains the first symptom of cerebellar tumors in many patients.\(^{11}\) Buch\(^{12}\) analyzed 48 children and confirmed that childhood AACE had a small but significant association with intracranial disease. The author found that age of onset of more than 6 years, papilledema, a significant angle deviation at a distance (>40%), and the recurrence in a child with hyperopia are the risk factors for AACE with intracranial disease. It is recommended that every patient with AACE be screened for neurological diseases, especially young children.

The treatment of AACE includes prismatic correction and binocular single vision training, injection of botulinum toxin, and surgery. The purpose of the surgery is to correct esotropia, eliminate diplopia, correct motor function, and recover sensory function. However, the optimal design for surgery is controversial. Wan and Savino\(^{13,14}\) proposed that target deviation is difficult to correct accurately, and there is a tendency for recurrence after surgery due to the “eating-prism phenomenon.” Ali\(^8\) proposed that an additional 10 PD augments the residual esophoria in most AACE patients and surgical target angle. In this study, 39 patients required surgery, and the postoperative outcome was satisfactory. We recommend that the surgery be fully corrective and designed according to the maximum preoperative angle. The satisfactory

![Figure 2: Comparison of the importance of the following risk factors for acute acquired concomitant esotropia: age, sex, spherical equivalent refraction, failure to wear glasses, and amount of near work per day. Near work per day was ranked to be the most important factor. The red dots represent the differences in statistical significance, as shown in Table 4](Image 55x527 to 557x731)
ocular position is exophoria at distance and esophoria at near vision.

The following three proposals aim to reduce surgical undercorrection and find the full latent deviation. The angle of strabismus needs to be measured multiple times on different occasions before surgery. Thus, the surgical plan can be designed using the largest and most stable angle. Prism adaptation is another effective measure. Press-on prisms can be used according to the distance deviation, with the patient using this prescription for 1–2 weeks. If there is residual esotropia, the strength of the press-on prisms can be increased, followed by another adaptation period of 1–2 weeks. This repetitive process would continue until the power of the prism is stable. The surgical plan relies on full prism-adapted power. Intraoperative adjustable sutures are also very effective, allowing the use of sufficient local anesthesia to achieve adjustment of ocular position during surgery.

Conclusion

In conclusion, multiple factors are associated with type III AACE. Increased hours of near work per day and uncorrected myopia in near work are independent risk factors for type III AACE in multivariate logistic regression models. A satisfactory result can be obtained by designing the foot correction with the maximum and most stable angles before surgery.

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Conflicts of interest
There are no conflicts of interest.

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