Risk factors analysis of consecutive exotropia
Oblique muscle overaction may play an important role

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Abstract
To evaluate clinical factors associated with the onset of consecutive exotropia (XT) following esotropia surgery.

By a retrospective nested case-control design, we reviewed the medical records of 193 patients who had undergone initial esotropia surgery between 2008 and 2015, and had follow-up longer than 6 months. The probable risk factors were evaluated between groups 1 (consecutive XT) and 2 (non-consecutive exotropia). Pearson chi-square test and Mann-Whitney U test were used for univariate analysis, and conditional logistic regression model was applied for exploring the potential risk factors of consecutive XT.

Consecutive exotropia occurred in 23 (11.9%) of 193 patients. Patients who had undergone large bilateral medial rectus recession (BMR) (\(P = 0.017\)) had a high risk of developing consecutive XT. Oblique dysfunction (\(P = 0.001\)), adduction limitation (\(P = 0.000\)) were associated with a high risk of consecutive XT, which was confirmed in the conditional logistic regression analysis. In addition, large amount of BMR (6 mm or more) was associated with higher incidence of adduction limitation (\(P = 0.045\)). The surgical methods and preoperative factors did not appear to influence the risk of developing consecutive XT (\(P > 0.05\)).

The amount of surgery could be optimized to reduce the risk of consecutive XT. The presence of oblique overaction and postoperative adduction limitation may be associated with a high risk of consecutive XT, which may require close supervision, and/or even earlier operation intervention.

Abbreviations: BMR = bilateral medial rectus recession, CI = confidence interval, DVD = dissociated vertical deviation, ET = esotropia, HR = hazard ratio, IOOA = inferior oblique muscle overaction, ORs = odds ratios, PD = prism dipters, SE = spherical equivalent, SO = superior oblique, SOOA = superior oblique muscle overaction, XT = exotropia.

Keywords: consecutive exotropia, oblique dysfunction, strabismus, surgery

1. Introduction
Consecutive exotropia (XT) is a manifest exotropia that develops either spontaneously or after optical or surgical treatment in a patient that formerly had esotropia (ET).

It has been reported in 4% to 27% of patients after treatment in a patient that formerly had esotropia.\(^1\-^6\) Although predating the occurrence of consecutive XT prior to esotropia surgery is difficult, probable risk factors include amblyopia, high hypermetropia, presence of A- or V- patterns, dissociated vertical deviation (DVD), postoperative limitation of adduction, various surgery methods, absent or poor binocularity and iatrogenic causes.\(^1\-^10\)

The cyclovertical muscles have a triple function that includes a vertical, torsional, and horizontal action. Generally, the superior oblique has a stronger vertical action than the inferior oblique, and oblique muscle overaction is not usually present at birth, but develops after 1 year of age. Primary ones may occur with no reason.\(^11\) In our clinic, some consecutive XT patients developed oblique dysfunction at the follow-up, which has not previously been reported to be a risk factor or early sign of consecutive XT. Therefore, the current study was conducted to investigate possible risk factors for consecutive XT.

2. Methods
This study was approved by the Institutional Review Board of West China Hospital. The medical records of all patients who had undergone esotropia surgery by a single surgeon between January 2008 and June 2015 were reviewed retrospectively. The exclusion criteria included history of eye surgery, other ocular diseases, patients with developmental delays, patients born prematurely or with other syndromes, and cases with postoperative follow-up periods of less than 6 months. Patients with preoperative oblique muscle dysfunction and A- or V- patterns were also excluded. Preoperative assessments included visual acuity, cycloplegic refraction (using 0.5% compound tropicamide or atropine), ocular anterior segment and dilated fundus evaluation, measurement of the ocular deviation for near and distance with correction, and examination of ocular motility.
2.1. Grouping

For exploring potential risk factor of consecutive XT, we applied nested case-control design for the data analyses. We allocated all patients who developed consecutive XT at the last follow up into the case group (Group 1), and used 1:4 matching for sex, age at onset of esotropia, and age at esotropia surgery to select the control group (Group 2). Group 1 (consecutive XT), consisted of patients with exodeviations ≥ 10 prism diopters (PD) measured at least once either at near or distance at 1 month or more postoperatively. Group 2 (non-consecutive XT) was comprised of patients with exodeviations < 10 PD, orthotropia or esodeviation by 1 month postoperatively.

2.2. Factors associated with onset of consecutive XT

The risk factors analyzed for consecutive exotropia are shown in Table 1.

**Amblyopia** was defined as a difference of more than 2 lines between the 2 eyes of best-corrected visual acuity or best-corrected visual acuity of each eye lower than 20/33, or absence of central, steady, maintained fixation. Each angle of deviation was primarily measured by alternate prism-and-cover test using accommodative targets at distance (5m), near (33 cm), upgaze, and downgaze. A modified Krimsky light reflex test was used to detect the angle of deviation for a few uncooperative patients.

**Oblique dysfunction** is the underaction or overaction of the oblique muscles. The difference in rotation of 1 eye relative to the other is noted as underaction or overaction, which is always associated with A- or V-patterns.[12] A vertical deviation is graded on a scale of −4 (underaction) to +4 (overaction), with 0 being normal. The degree of oblique muscle overaction could be measured using photographs of the cardinal positions of gaze with minimal observer dependency.[13]

**Limitation of adduction** was recorded postoperatively and graded on a scale of −1 to +4: −4 indicated no movement beyond midline; −3 indicated that 25% of movement remained; −2 indicated that 50% of movement remained, and −1 indicated that 75% of movement remained.[4]

**The surgical methods** were mainly divided into 2 categories: the symmetrical procedure or asymmetrical operation.[6] For exotropia (ET) that was greater at near or approximately the same at distance and near, patients underwent bilateral medial rectus recession (BMR) surgery. For ET that was greater at distance, bilateral lateral rectus muscle resection was conducted. For deviations < 20PD, monocular surgery was performed in patients who had amblyopia and no alternation.

Patients were also categorized into 5 subgroups in terms of spherical equivalent (SE): emmetropia and myopia, 0 ≤ SE ≤ +2.0D, +2.0 ≤ SE ≤ +4.0D, +4.0 ≤ SE ≤ +6.0D, and > +6.0D. Oblique dysfunction was categorized as: normal, superior oblique muscle overaction, inferior oblique muscle overaction, superior oblique muscle palsy, and inferior oblique muscle palsy.

2.3. Statistical analysis

The Pearson chi-square test (if expected frequency in more than 20% of cells was < 5 or < 1 in any cell, using Fisher exact test) or the Mann–Whitney U test was used as univariate analyses to compare difference between case and control groups. To further explore potential risk factors of consecutive XT, we applied conditional logistic regression model. We calculated odds ratios (ORs) and their 95% confidence interval (CI) were used to estimate magnitude of effects. We used the data of latest follow up in all analyses and several missing data were not special handled. All analyses were performed with SPSS 22.0 software (IBM (International Business Machines Corporation), New York, United States).

3. Results

Two hundred and thirty-seven patients were identified and 193 patients had complete data at the 6 months endpoint. Patient flow chart is shown in Fig. 1. The eligible patients had a median follow up of 21 months (range, 6–91 months). Consecutive XT occurred in 23 (11.9%) of the 193 patients, and the 1:4 matched control group included 92 patients. In addition, 14 cases of esodeviation were observed in the total 193 patients. The clinical features of all cases included in the study are shown in Table 1.

3.1. Factors statistically significantly associated with the onset of consecutive XT

The amount of BMR, oblique muscle overaction after the ET surgery, and adduction limitation were statistically significantly correlated with onset of consecutive XT.

3.1.1. Acquired oblique dysfunction. Thirteen (56.5%) of 23 consecutive XT patients in group 1 developed new oblique dysfunction, including 9 patients with superior oblique muscle overaction (SOOA), 3 patients with inferior oblique muscle overaction (IOOA), and 1 patient with superior oblique (SO) palsy. Eight (8.7%) of the 92 patients in group 2 developed new oblique dysfunction, including 3 with SOOA, 1 with IOOA, and 4 with SO palsy. The difference between the 2 groups was statistically significant (P = 0.001).

3.1.2. Adduction limitation. Eight (34.8%) patients in group 1 and 3 (3.3%) patients in group 2 had adduction restriction postoperatively. The difference between the 2 groups was statistically significant (P = 0.000). In addition, a significantly higher incidence of adduction limitation was found to be associated with the amount BMR (P = 0.045) (Table 2). The association between amount of BMR and the occurrence of consecutive XT was statistically significant (P = 0.017).

![Figure 1. Patient flow chart. XT = Exotropia.](chart.png)
The logistic regression analysis indicated a hazard ratio (HR) of 11.327 with a 95% CI of (1.928–66.531) for SOOA and an HR of 16.496 with a 95% CI of (1.474–184.630) for adduction limitation (Table 3).

3.2. Factors statistically insignificant with the onset of consecutive XT

No statistically significant difference was found between the groups in terms of presence of amblyopia, refractive error, preoperative angle of deviation, or surgical methods. The spherical equivalent results between the 2 groups were not statistically significant among any of the 5 subgroups ($P = 0.638$).

3.2.1. Surgery method. Most of the patients underwent symmetric surgeries. The comparison between the 2 groups was insignificant statistically ($P = 0.690$).

3.3. Exotropia stage of the 23 consecutive XT patients

Of the 23 consecutive XT patients, the mean angle of exodeviation was $-30.87 \pm 11.20$ PD (range, $-10$ to $-65$ PD) at near and $-27.22 \pm 10.40$ PD (range, $-10$ to $-55$ PD) at distance. The mean interval between the initial surgery and the XT operation was 37 (range, 1–90) months. For the 13 patients with oblique dysfunction, 4 patients combined with A- or V-patterns, including 3 A-patterns and 1 V-patterns.

4. Discussion

Consecutive XT is still a frequent problem with various risk factors. The 11.9% incidence of consecutive XT after ET surgery found in the current study is similar to the incidence rates of 4% to 27% reported in previous studies.[3,7,8]

4.1. Factors statistically significant correlated with consecutive XT

Thirteen (56.5%) of the 23 consecutive XT patients developed oblique dysfunction. The difference between group 1 and group 2 was statistically significant and patients with SOOA at the follow-up were especially likely to develop consecutive XT. It could be that oblique muscle overaction may already exist in the primary ET patients, but was not found before the initial ET surgery. One reason for this could be that some patients do not cooperate with the examination, especially some infants with large angle

| Table 1 |
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| **Probable factors associated with onset of consecutive exotropia.** |
| **Variables** & **Group1** & **Group2** & **$P$** |
| Preoperative factors & & & |
| Sex (male:female) & 11:12 & 44:48 & 1.000$^*$ |
| Age at onset, y & 2 [0–9] & 1 [0–10] & 0.383$^{**}$ |
| Age at surgery, y & 5 [1–13] & 4 [2–13] & 0.436$^{**}$ |
| Duration from onset to surgery, y & 3 [0.3–12] & 2 [0.2–10] & 0.675 |
| Amblyopia & 12/23 (52.2%) & 43/92 (46.7%) & 0.641 |
| Spherical equivalent & & & 0.638$^{**}$ |
| Preoperative deviation (PD) & & & |
| At distance & 45 [15–120] & 50 [18–110] & 0.171$^{**}$ |
| At near & 45 [15–105] & 55 [25–100] & 0.144$^{**}$ |
| Surgical factors & & & |
| Type of eye muscle surgery & Symmetrical & 8 [0.3–12] & 88.9% | 0.690$^{***}$ |
| Asymmetrical & 2 [8.7%] & 11 [12%] & |
| Amount of BMR recession & $\geq 6$ mm & 14 [63.6%] & 0.017$^*$ |
| <6 mm & 8 [36.4%] & 56 [64.4%] & |
| Postoperative factors & & & |
| Angles of deviation at postoperative 1 wk (PD) & & & |
| At distance & 3 [–10–10] & 3 [–10–10] & 0.412$^{**}$ |
| At near & 2 [–10–10] & 1 [–10–10] & 0.861$^{**}$ |
| Adduction limitation & 0 [0–2] & 0 [0–3] & 0.000$^{**}$ |
| The acquired oblique dysfunction & SOOA & 9 [39.1%] & 0.001$^{***}$ |
| IOOA & 3 [13.0%] & 1 [1.1%] & |
| Superior oblique palsy & 1 [4.3%] & 4 [3.3%] & |

Group 1 (consecutive exotropia): exodeviation $\geq 10$ PD by 1 month postoperatively; Group 2 (non-consecutive exotropia): exodeviation $< 10$ PD, orthotropia or esodeviation, measured at least once either at near or at distance at 1 month or more postoperatively.

BMR = bilateral medial rectus recession, IOOA = inferior oblique muscle overaction, PD = prism diopters. SOOA = superior oblique muscle overaction.

$^*$ Chi-square test.

$^{**}$ Mann–Whitney $U$ test (data are present as median and range).

$^{***}$ Fisher exact test.

The logistic regression analysis indicated a hazard ratio (HR) of 11.327 with a 95% CI of (1.928–66.531) of SOOA and an HR of 16.496 with a 95% CI of (1.474–184.630) of adduction limitation (Table 3).

| Table 2 |
| --- |
| **The correlation between amount of bilateral medial rectus recession and adduction limitation.** |
| The amount of BMR & Adduction limitation (+) & $P$ |
| $\geq 6$ mm & 8/44 (18.2%) & 0.045$^{***}$ |
| <6 mm & 2/64 (3.2%) & |

BMR = bilateral medial rectus recession.

$^{***}$ Fisher exact test.
esotropia. Another possible reason is that ocular torsion may contribute to A or V patterns and over-elevation or over-depression in addition. Objective torsion is reported in children with infantile esotropia, long before they develop over-elevation in abduction.[14]

Oblique overaction may also develop after ET surgery. Abduction is the tertiary action of the oblique muscles and overaction of oblique muscles leads to over-abduction. Such incompatance in up- and downgaze causes instability of the eyes and esotropia on depression or elevation. Folk demonstrated that many patients showed an exodeviation in the straight up or straight down position prior to developing a deviation in the primary position.[10] In addition, the incompatance may prevent the development of binocular function, thus leading to the gradual development of consecutive XT after ET surgery, with or without A- or V-patterns.[21] For example, in the case of SOOA, children often look down for a long time when they study or play games. The overaction of superior oblique muscles would then continuously induce abduction, leading to instability of orthotropia and difficulty in the development of binocular function. As other studies have illustrated, binocular function promotes stability of alignment after surgery in the long-term.[15–17] Moreover, Bradbury illustrated that postoperative binocular function, rather than preoperative, was a significant factor in the development of consecutive XT.[4] Postoperative oblique overaction is not beneficial for long-term alignment and may even accelerate the development of misalignment.

Furthermore, in addition to ophthalmoscopic examination, fundus photography should be done to further evaluate the eyes and to provide a record of torsion. Moreover, it is suggested that training in binocular function be done in patients both pre- and postoperatively, though preoperative training may not be a significant factor. Synoptophore, Disc Synoptoscope, and Behavioral training like videogames could be conducted to help building their binocular function.[18–21] Finally, since the reasons for development of oblique dysfunctions are rather complex, patients with such signs after the initial ET surgery, especially SOOA, may require close supervision, and/or even earlier surgical interventions. In a future study, magnetic resonance imaging examinations may be performed to examine the factors involved in the development of superior oblique overaction after the ET surgery next.

Limitation of adduction was a statistically significant risk factor associated with development of consecutive exotropia, as other studies have illustrated.[3,6] It could be argued that one of the factors responsible might be the surgical technique employed in some patients (large recessions of ≥6 mm, including 6, 6.5, 7 mm). In this study, the amount of BMR was significantly correlated to the incidence of adduction limitation. It could be beneficial to operate on 3 or 4 rectus muscles for large angle deviations and to limit surgery on the medial rectus.[7] Another factor that might play a role is medial rectus slippage. It could be mostly happened in small BMR recession. Demer found that 1/3 of patients with consecutive XT also exhibited medial rectus muscle slippage, similar to the results of study by Cho and Ryu, which found an incidence of 22% slippage associated with limited adduction.[22] But this may not have been a major factor in this study due to different suture methods. The suture knot was not only reattached to the sclera of new insertion sites, but across the muscle and knotted on the recesional muscle surface. This might be beneficial for the absorption of suture, while also strengthening the resewn suture. However, we did not examine every recessed medial rectus.

4.2. Factors not statistically significantly correlated with consecutive XT

As the age was matched in the study, there was no statistically significant difference between the 2 groups. Whether amblyopia is a risk factor for the development of consecutive XT remains controversial. In contrast to previous studies,[6,10] Iyengar[3] indicated that amblyopia did not increase the risk for consecutive XT. Similarly, it is not a statistically significant factor in developing consecutive XT in the present study.

Patients with hypermetropia have been shown to develop consecutive XT even without surgery.[23,24] Furthermore, a higher risk of developing XT has been shown in hypermetropic patients with a decreased ability for accommodative convergence during long-term follow-up.[23] However, the presence of simple hypermetropia was not a risk factor for developing secondary XT in our study, similar to some other studies[4,10] and, therefore, may not an independent risk factor for the development of consecutive XT.

When comparing the incidence of consecutive XT between patients that have undergone different surgical methods, some studies have shown that symmetrical surgery may not be the most suitable procedure and that the adduction limitation occurred more frequently after asymmetrical surgeries.[6] However, some have noted asymmetrical surgery as a risk factor for consecutive XT.[3] The negative results in the current study may be because most of the patients underwent symmetrical surgeries.

There are some limitations in this study that may affect the strength of the findings. The retrospective design may lead to potential information bias. The rating scale of vertical deviation was usually determined by an ophthalmologist with more than 5 years of clinical experience, and then checked by a pediatric ophthalmologist with more than 20 years of clinical experience. However, the objective measurement as reported by Lim et al.[13] was not used in this retrospective study. Thus, prospective, long-term studies would help confirm these findings, and the oblique muscle overaction could be examined by the quantitative method to help improve clinical diagnosis. In conclusion, the amount of BMR should be decreased in order to reduce the risk of consecutive XT. Furthermore, patients with signs of oblique

Table 3

| Variables                  | Standard error | P     | Hazard ratio | 95% CI          |
|----------------------------|----------------|-------|--------------|-----------------|
| Adduction limitation       | 1.232          | 0.023 | 16.496       | 1.474–184.630   |
| Acquired SOOA              | 0.903          | 0.007 | 11.327       | 1.928–66.531    |
| Acquired IOOA              | 1.210          | 0.079 | 8.349        | 0.780–89.405    |
| Superior oblique palsy     | 1.224          | 0.477 | 2.389        | 0.217–26.291    |

CI= confidence interval; IOOA= inferior oblique muscle overaction; PD= prism diopters; SOOA= superior oblique muscle overaction.
overaction and/or postoperative adduction limitation should be closely supervised and/or earlier surgical intervention should be considered.

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