Subtle Vertical Deviation in Intermittent Exotropia

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Abstract

**Background**: To detect the subtle vertical deviation in patients with intermittent exotropia (IXT) by using prism and alternate cover test, synoptophore and perceptual eye position (PEP) test.

**Methods**: An observational cross-sectional study was conducted of 104 IXT patients and 128 controls. A detailed ophthalmic examination was conducted on each participant. Eye position was evaluated by prism and alternate cover test, synoptophore and PEP test. Stereoacuity was measured by the Randot stereoacuity test for both near and medium distances.

**Results**: The abnormality ratio of subtle vertical deviation was significantly higher as measured by the PEP test than by synoptophore, prism and alternate cover test (PEP: 47.12%, synoptophore: 2.88%, prism and alternate cover test: 1.92%, \( P < 0.001 \)). Furthermore, medium distance and near stereopsis were better in patients with normal vertical eye position than those with abnormal vertical eye position (\( P = 0.004 \) and \( P=0.017 \), respectively). No statistic differences were found between two groups both in near and far horizontal deviation measured by prism and alternate cover test (\( P=0.527 \), \( P=0.376 \)). There were no significant differences in age, interocular difference in spherical equivalent (SE) between two groups (\( P=0.186 \) and \( P=0.117 \), respectively).

**Conclusions**: An abnormal subtle vertical deviation is detected by PEP test in some patients with IXT, which is difficult to be measured by prism and alternate cover test, synoptophore. The stereoacuity is impaired by the abnormal subtle vertical deviation, rather than other factors such as age, horizontal deviation and anisometropia.

**Background**

Intermittent exotropia (IXT) is a form of early onset childhood strabismus that occurs increasing frequency in Asian populations [1, 2]. In China, the most common form of strabismus is IXT, which accounts for 77.8% of children with strabismus [3]. It typically begins as exophoria that progresses to intermittent deviation [2]. The initial symptoms present as abnormal distance fixation during periods of tiredness or inattention. However, it may become more frequent and begin to occur during near fixation, with some cases eventually developing exotropia. Deviation of eye position is one of important characteristics of IXT. The combination of a hypertropia coexisting with intermittent exotropia was common in clinical practice, which was related to dissociated vertical deviation (DVD), oblique dysfunction or paretic muscle. In addition to this, a small number of IXT patients presented a hypertropia with unknown mechanisms [4]. Only a few studies have focused on the vertical deviation with unknown reasons that coexisted with intermittent exotropia. With the development of methods for detecting ocular alignment, it is possible to find more vertical deviation with unknown reasons in IXT which may be underestimated before.

In the clinic, Hirschberg test, cover test, or synoptophore are usually performed as routine examinations to evaluate IXT. The perceptual eye position (PEP) test is a new method for the assessment of binocular
alignment, which uses a computer-controlled perceptual evaluation system to determine fixation disparity and binocular function [5]. Unlike traditional approaches using the Hirschberg test and cover test, PEP is measured under conditions of dichoptic vision. Furthermore, a computer records PEP pixels to precisely quantify binocular misalignment. The smallest unit of binocular misalignment that can be determined by computer-controlled ocular misalignment software is one pixel, compared with one prism when using synoptophore, which is the equivalent of 25 pixels. The present study we measure previously overlooked subtle vertical deviation accompanied with IXT and analyze the association between subtle vertical deviation and stereoacuity.

Methods

Participants

This was an observational cross-sectional study. A total of 104 patients with IXT (ages 3 to 28 years old) seen at the outpatient clinic of the Beijing Tongren Hospital between July 2016 and February 2017 were enrolled. For the control group, 128 asymptomatic age- and gender-matched normal subjects were recruited during the same period. This study was approved by the ethics committee of the Beijing Tongren Hospital Institutional Review Board at Capital Medical University (ChiCTR1800018005).

Inclusion criteria were (1) IXT patients with detectable superposition and (2) best corrected visual acuity of 0.8 or better in each eye. Exclusion criteria were (1) clinically significant vertical deviations, which was defined as a magnitude of 5 prism dioptres or greater in primary position [4]; (2) anisometropia of 2.50 dioptres or greater; (3) incomitance of horizontal or vertical deviation; (4) significant oblique muscle over action; (5) dissociated vertical deviation (DVD); (6) any concurrent eye disease; (7) patients unable to undergo measurement by either synoptophore or the PEP test; or (8) a history of strabismus surgery [6]; (9) neurologic disorders. All the patients wore their corrective lens for the measurements. Systematic eye examinations were performed by certified orthoptists and ophthalmologists. The examiners were blinded to the measurements.

Measurement of ocular alignment

The ocular alignment of IXT patients were measured by prism and alternate cover test, PEP test and synoptophore. PEP test and synoptophore were performed at the same visit and the order of these testing was randomized.

Measurement of perceptual eye position

The PEP tests were administered according to previously described protocols [5]. The minimum unit of ocular misalignment obtained by the computer-controlled ocular misalignment system was one pixel. The assessment included horizontal and vertical ocular misalignment.

Measurement of superposition
Superposition, fusion, and stereovision distance were measured using a synoptophore L-2510B/L-2510HB machine (Inami & Co., Ltd., Japan). Synoptophore superposition means the coverage of one examination picture with the second. The pictures were tiger (H9.5, V6.5) and cage (H11.5, V7.5).

Assessment of stereoacuity

Near stereoacuity was measured by the Randot stereoacuity test. The test was administered according to previously described protocols [7]. Scores were converted to log seconds of arc for analyses. The Randot test was performed at 40 cm and tested at disparities of 800, 400, 200, 140, 100, 80, 60, 50, and 40 seconds of arc. Two of three correct responses were required to pass each disparity level. Patients who were unable to identify shapes at the 800 seconds of arc level were recorded as having nil stereo. For analyses, nil stereo was assigned as the next highest log level, that is, 3.20 log seconds of arc [8] (Table 1).

Medium distance stereoacuity

The devices used to measure medium distance stereoacuity included: Windows XP system PC host, LG2342p polarized 3 dimension (3D) monitor with a resolution power of 1920×1080 and refresh frequency of 120 Hz, and 3D polarized glasses. The examination system of the National Engineering Research Center for Healthcare Devices was used. The midpoint of the monitor was held 80 cm away and at the same height as the patients’ eyes. Stereoacuity was measured by identification of the E shape. The random dot background was 5°×5°and the E shape was 3°×3°in size. The Randot test was used to measure disparities of 400, 300, 200, and 100 seconds of arc. Patients who were unable to identify shapes at the 400 seconds of arc level were recorded as having nil stereo. For analyses, nil stereo was assigned as the next highest log level, that is, 2.9 log seconds of arc (Table 2).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows (ver. 22.0. IBM Corp, Armonk, NY). Gender comparisons between IXT patients and normal controls, abnormality ratios of misalignment in IXT patients determined by synoptophore and the PEP tests were made using the $\chi^2$ test. Age comparisons between IXT patients and normal control, comparisons of stereoacuity, interocuclar difference in SE and age between the two groups (normal versus abnormal vertical PEP) were made using the independent sample T test. Missing data were handled through deletion. A P-value <0.05 was considered statistically significant for all analyses.

Results

Demographics of patients

In the present study, 104 IXT patients were recruited along with 128 age- and gender-matched case controls. The mean age of the IXT patients and controls were 8.40 ± 3.89 years (range from 3 to 28 years)
and 9.20 ± 2.80 years (range from 4 to 26 years), respectively ($P = 0.072$). There were 48 males (46.15%) and 56 females (53.85%) in the IXT group and 63 males (49.22%) and 65 females (50.78%) in the control group ($P = 0.642$).

The mean horizontal deviation (prism dioptres, PD) in patients with IXT was -32.93 ± 14.70 (range -105 to -10) at near and -33.02 ± 13.50 (range -105 to -15) at distance by using prism and alternate cover test.

**Eye position deviation as measured by synoptophore and the PEP test in normal**

We first measured the horizontal and vertical eye positions of normal controls using both synoptophore and the PEP tests. The mean horizontal eye deviation was -0.34±1.95° in synoptophore and 28.09±32.81 pixels in PEP. The mean vertical eye deviation was 0.03±0.15° in synoptophore and 4.29±4.28 pixels in PEP (Fig. 1A). The normal ranges were calculated using these values by mean±1.96 SD. Thus, the normal horizontal eye position ranges were -4.16~+3.48° versus 0~92.40 pixels; the vertical eye position ranges were 0~0.32° versus 0~12.68 pixels, as measured by synoptophore and PEP tests, respectively.

**Subtle vertical misalignment measured by prism and alternate cover test, synoptophore and the PEP test in patients with intermittent exotropia**

Among 104 IXT patients, there were two patients (1.92%) who had accompanied vertical misalignment (3△ and 4△, respectively) measured by prism and alternate cover test. And synoptophore detected only three patients (2.88%) with vertical deviation larger than 0.5°. However, there were 44 cases with concurrent vertical misalignment greater than 13 pixels and 5 patients who showed interocular suppression as measured by the PEP test (Fig. 1B). The abnormality ratio of subtle vertical misalignment was significantly greater as measured by the PEP test than by prism and alternate cover test, synoptophore (PEP: 47.12% versus prism and alternate cover test: 1.92%, synoptophore: 2.88%, $P<0.001$). The mean vertical misalignment for the 44 cases with abnormal vertical deviation and 55 cases with normal vertical deviation were 46.05±38.36 pixels (14~179 pixels) and 5.20±3.21 pixels (0~13 pixels), respectively.

**Difference of clinical profiles between patients with normal and abnormal vertical PEP**

Of 104 IXT patients, PEP detected 49 cases with abnormal vertical deviation and 55 cases with normal vertical deviation. Both groups underwent additional examination to determine whether vertical deviation affected stereoacuity. The mean near stereoacuity in patients with normal and abnormal vertical PEP test were 2.21±0.34 and 2.40±0.44, respectively (Fig. 2A). The mean medium distance stereoacuity in patients with normal and abnormal vertical PEP test were 2.09±0.23 and 2.25±0.31, respectively (Fig. 2B). Patients with abnormal vertical PEP test had significant worse near and medium distance stereoacuity than those of normal vertical PEP test ($P=0.017$, $P=0.004$).

The mean age in patients with normal and abnormal vertical PEP test were 8.87±4.03 and 7.85±3.68, respectively. There was no significant difference between two groups ($P=0.186$) (Fig. 3). The mean
horizontal deviation (prism dioptres, PD) in patients with normal and abnormal vertical PEP test were -32.06±15.91 vs -34.02±13.14 for near deviation (Fig. 4A), -31.90±14.53 vs -34.39±12.16 for far deviation (Fig. 4B), respectively. No statistic differences were found between two groups both in near and far deviation (P=0.527, P=0.376).

The mean value of bilateral differences in spherical equivalent (SE) was 0.44±0.50 D for patients with normal vertical PEP and 0.31±0.32 D for those with abnormal vertical PEP. No significant differences were found between the two groups (P = 0.117) (Fig. 5). These results indicated that the difference in stereoacuity was caused by subtle vertical deviation and rather than other factors such as age, horizontal deviation and anisometropia. Taken together, it suggests that abnormal subtle vertical PEP can affect stereopsis in IXT patients.

**Difference of stereoacuity between IXT patients and normal controls**

The mean near stereoacuity in IXT patients and normal controls were 2.30±0.40 and 2.02±0.22, respectively (Fig. 6A). The mean medium distance stereoacuity in patients and normal controls were 2.16±0.28 and 2.04±0.10, respectively (Fig. 6B). IXT patients had significant worse near and medium distance stereoacuity than those of normal controls (P<0.001, P<0.001). In order to conduct further analysis, IXT patients with normal and abnormal vertical PEP test were compared with normal controls separately. The near stereoacuity of patients with normal vertical PEP test was significantly worse than those of normal controls (2.21±0.34, 2.02±0.22, P<0.001) (Fig. 2A). Although the medium distance stereoacuity of patients with normal vertical PEP test was worse than those of normal controls, the difference was not statistically significance (2.09±0.23, 2.04±0.10, P=0.067) (Fig. 2B). Both the near and medium distance stereoacuity of patients with abnormal vertical PEP test were significantly worse than those of normal controls (near: 2.40±0.44, 2.02±0.22, P<0.001; medium: 2.25±0.31, 2.04±0.10, P<0.001) (Fig. 2).

**Discussion**

Intermittent exotropia (IXT) is a common form of childhood strabismus [9] with a variety of clinical symptoms. Previous studies reported vertical deviation frequently coexisted with exotropia [10]. The mainly reasons for hypertropia include superior oblique muscle palsy (SOP), DVD, inferior oblique overaction (IOOA) and paretic muscle. Even if hypertropia caused by common reasons has been excluded, vertical deviation still presents in some patients with IXT. Struck and Daley reported 16% IXT patients manifested clinical significant hypertropia with a magnitude of 5 PD or greater, unrelated to DVD, oblique dysfunction or paretic muscle [4]. The cause for the hypertropia is still unclear. The possible reason is that IXT patients have an asymmetric innervation input from the two compartments of lateral rectus muscle [11].

In our study, we focused on subtle hypertropia which is frequently neglected in IXT patients. It is difficult to identify such subtle vertical deviation by prism and cover test, and synoptophore.
When ocular alignment is assessed using the prism and alternate cover test, the examiners change prism strength until no refixation movement is seen. It was reported that strabismus impairs the ability to fixate targets steadily and fluctuations of ocular deviation were present in exotropia. Fluctuations presented both on a brief time scale and on a longer time scale (seconds to minutes). It raises the possibility that 2 prisms of a slightly difference power may abolish the refixation movement [12], which may make it difficult to detect the subtle vertical deviation in patients with IXT.

Another possible reason for the difference between prism alternate cover test, synoptophore and PEP test in detecting vertical deviation was that synoptophore and PEP test were carried out under binocular dichoptic vision. Although both PEP and synoptophore are measured under binocular dichoptic vision, substantial differences in detecting vertical deviation were also present. The possible reasons are relatively smaller fixation test-object and the more precise minimum unit (1 pixel) controlled by computer are used in PEP, which make it easier to reveal subtle changes of ocular misalignment.

Of note, additional evidence indicates that IXT occurs more commonly with refractive error [13–15] and the instability of vertical PEP may be associated with the severity of anisometropia [5]. In order to exclude the influence of anisometropia, patients with binocular difference in SE of 2.50 dioptres or greater were ruled out. Besides this, there was no significant difference in the bilateral refractive errors between patients with normal vertical PEP and those with abnormal vertical PEP, which suggested the instability of vertical PEP in IXT patients was not caused by anisometropia.

Although the subtle vertical deviation measured by PEP test was too small to be of clinical significance, it may potentially help to shed light on underlying sensory mechanism for stereoacuity in IXT patients. Previous study showed some postoperative IXT patients with clinically normal stereoacuity and visual acuity still had sensory eye imbalance, even after they were orthotropic or having a horizontal heterotropia of 10 prism diopters or less [16]. Furthermore, our results showed some IXT patients accompanied with subtle vertical deviation which is not easy to detect by prism had worse stereoacuity. It suggests more attention should be paid to sensory binocular processing and binocular stability.

Our results showed IXT patients without subtle vertical deviation had worse near stereoacuity than those of normal control, while there was no significant difference in medium distance stereoacuity even if the value of medium distance stereoacuity was worse in IXT patients. The possible reason was that there were only 5 levels for medium distance stereoacuity (nil, 400, 300, 200, and 100 seconds of arc), which was less than the near stereoacuity measurement. The less levels of medium distance stereoacuity may have contributed to our failure to find the difference between IXT patients without subtle vertical deviation and normal controls especially when the difference is small. IXT patients had worse stereoacuity compared with normal people, with or without subtle vertical deviation. The difference between IXT patients without subtle vertical deviation and normal controls was greater than that between patients with subtle vertical deviation and normal people, which probably reflects the impact of subtle vertical deviation on stereoacuity.
Our study has some limitations. Exodeviation control was not measured. Recently research has suggested stereoacuity, control and angle of deviation of intermittent XT have been shown to have weak or moderate association with each other [17]. Even though we found the difference in stereoacuity was not caused by horizontal deviation, which was consistent with recent study [17], whether subtle vertical deviation is associated with control remains to be clarified. Although the difference in the stereoacuity was statistically significant for near and medium distance, the degree of difference between IXT patients with normal and abnormal vertical PEP was quantitatively small. Superstein et al thought each clinical characteristic should be considered separately for an individual IXT patient [17]. The stereoacuity might be affected by the combination of many factors such as control, vertical deviation and other unknown factors, which explains to some extent why the degree of difference in stereoacuity was small. In addition, measurements of ocular alignment, stereoacuity are variable in IXT patients [8]. Whether the magnitude of difference of stereoacuity is clinically significant should be further confirmed by more researches. Nevertheless, small vertical deviation of unknown origin in these patients can add another dimension to understand the physiology of binocular vision in IXT patients.

Some clinical controversies exist regarding the appropriate time for intervention and the most efficacious therapy for IXT [18, 19]. There is no consensus on which parameters are most important for the prognosis and progression of IXT [20]. And there are no general criteria for either non-surgical or surgical interventions in IXT patients [21–24], we will conduct additional follow-up testing with this population. These investigations will allow us to determine if the PEP test alone or in combination with other parameters can more comprehensively evaluate IXT, and whether these findings have predictive value for the therapeutic outcomes of different IXT treatments.

**Conclusions**

An abnormal subtle vertical deviation is detected by PEP test in some patients with IXT, which is difficult to be measured by prism and alternate cover test, synoptophore. Importantly, the very small vertical deviation is associated with stereoacuity, and displays a better stereoacuity in patients with normal vertical eye position than those with abnormal vertical eye position. The impaired stereoacuity is caused by the abnormal subtle vertical deviation, rather than other factors such as age, horizontal deviation and anisometropia.

**Abbreviations**

IXT: intermittent extropia;

PEP: perceptual eye position;

SE: spherical equivalent;

DVD: dissociated vertical deviation;
PD: prism diopters;
SOP: superior oblique muscle palsy;
IOOA: inferior oblique overaction;

Declarations

Ethics approval and consent to participate

All participants involved were informed of the purpose of this study. A written consent was obtained from their parents or legal guardians for participants under 18 years. Participants equal or above 18 years of age signed the informed consent by themselves. This study was approved by the ethics committee of the Beijing Tongren Hospital Institutional Review Board at Capital Medical University (ChiCTR1800018005).

Consent for publication

Not applicable.

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

JH participated the study design, collected the database, performed the statistical analysis and results analysis, and drafted the manuscript. JF carried out the study design, managed the experiments, participated in results analysis, editing and review of manuscript. NM, ZJM and BWZ helped in conducting experiments and data collection. HC designed the PEP test and provided the technical supports. All authors read and approved the final manuscript.

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Tables
Table 1
Levels of near stereoacuity showing equivalent Log seconds of Arc values

| Seconds of Arc | Log of seconds of Arc |
|----------------|-----------------------|
| 40             | 1.60                  |
| 50             | 1.70                  |
| 60             | 1.78                  |
| 80             | 1.90                  |
| 100            | 2.00                  |
| 140            | 2.15                  |
| 200            | 2.30                  |
| 400            | 2.60                  |
| 800            | 2.90                  |
| Nil stereo     | 3.20                  |

Table 2
Levels of medium stereoacuity showing equivalent Log seconds of Arc values

| Seconds of Arc | Log of seconds of Arc |
|----------------|-----------------------|
| 100            | 2.00                  |
| 200            | 2.30                  |
| 300            | 2.48                  |
| 400            | 2.60                  |
| Nil stereo     | 2.90                  |

Figures
Figure 1

Distribution of vertical deviation between control and IXT patients as detected by PEP test. PEP test was performed on 128 control cases (A) and 104 IXT patients (B) to examine vertical eye position. All values were included in the dot distribution graphs.
Abnormal vertical PEP affected near (A) and medium distance (B) stereoacuity in IXT patients. Near and medium distance stereoacuity were compared among IXT patients with normal vertical PEP, IXT patients with abnormal PEP and normal controls, *** $P < 0.001$. 

Figure 2
Figure 3

Comparison of age between IXT patients with normal vertical deviation and with abnormal vertical deviation using PEP test.

Figure 4

Comparison of near (A), far (B) horizontal deviation between IXT patients with normal vertical deviation and with abnormal vertical deviation using prism and alternate cover test.
Figure 5

Comparison of interocular difference in SE between IXT patients with normal vertical deviation and with abnormal vertical deviation.
Figure 6

Comparison of near (A) and medium distance (B) stereoacuity between IXT patients with normal controls, *** $P < 0.001$.

Supplementary Files

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