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Classification and misclassification of sensory monofixation in intermittent exotropia

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Abstract

Purpose—The course of intermittent exotropia (XT), and response to surgery, may depend on whether or not there is underlying monofixation. The purpose of this study was to report the prevalence of sensory monofixation in intermittent XT using different stereotests, and to determine the risk of misclassifying monofixation based on a single administration of each test.

Design—Retrospective case review of children with intermittent XT

Methods—Forty-four children were identified in whom Preschool Randot, Frisby, and Titmus stereoacuity were all measured at a single exam. Ninety-two children were identified with near stereoacuity measured on 2 sequential visits (Preschool Randot n=73, Frisby n=66 and Titmus n=40). Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds, bifixation was defined as at least 40 arcsec, and 'uncertain' as within normal range for age but worse than 40 arcsec).

Results—In children measured by all 3 tests on the same visit, sensory monofixation occurred in 36% using Preschool Randot, 48% using Titmus and 55% using Frisby (P>0.1 for each comparison). There was poor agreement between Frisby and Preschool Randot when classifying monofixation in individual patients (P=0.05). In children measured on sequential visits, misclassification occurred in 5% with Preschool Randot, 13% with Titmus and 23% with Frisby (Preschool Randot vs Frisby, P=0.005)

Conclusions—Classification of monofixation depends on the stereotest used. Regardless of stereotest, there is a risk of misclassifying monofixation on a single assessment. Potential misclassification needs to be considered in clinical practice and designing studies.

Introduction

Intermittent exotropia (XT) is often characterized by bifoveal fixation (bifixation) and normal near stereoacuity.[1-5] Nevertheless, a proportion of patients with intermittent XT demonstrate reduced near stereoacuity[2, 6] and have been described as having monofixation.[6, 7] The course of intermittent XT and response to surgery may depend on the presence or absence of underlying monofixation.[6, 7] (Sensory outcomes after surgery for intermittent exotropia Morrison D et al. Paper presentation, AAPOS 2009)

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When establishing the presence of monofixation in intermittent XT, Worth 4-dot and 4 diopter base-out testing are often confounded by the intermittency of the deviation and consequently, a diagnosis of monofixation relies primarily on the assessment of near stereoacuity. Ideally, a single measure of stereoacuity would accurately represent a patient's sensory status, but we have previously reported marked test retest variability of stereoacuity testing in children.[8, 9] Recently we noted that this variability may confound the diagnosis of monofixation in IXT. There are a number of factors which make a single measure of stereoacuity difficult to interpret: 1) stereoacuity thresholds may differ solely depending on the test used;[10] 2) stereo-thresholds in children with intermittent XT demonstrate poor test-retest reliability;[8] 3) there are a wide range of normal thresholds in young children,[11-15] and 4) dichotomizing the results of any continuous measure carries the risk of misclassification.[16] Despite these potential problems, clinicians often still use a single measure of near stereoacuity to define monofixation. The aims of this present study were to report the prevalence of monofixation in children with intermittent XT using three different tests of near stereoacuity (Preschool Randot [Stereo Optical Inc., Chicago, IL] Frisby [Frisby Stereotest Ltd, Sheffield, England] and Titmus [Stereo Optical Inc., Chicago, IL]) and to describe the risk of misclassifying monofixation with each test.

Methods

Children with intermittent XT (basic, true or pseudo divergence excess types) at a single institution were identified using a clinical database; children with convergence insufficiency type (near angle more than 10 prism diopters (pd) greater than distance) were excluded as were children with developmental delay or a sensory or paralytic form of exotropia. The stereotest(s) used on a specific examination depended on practitioner preference. We defined two patient cohorts: one cohort with all three stereotests used on a single examination to directly compare tests and a second cohort with sequential examinations using the same test to evaluate misclassification.

Stereoacuity testing

Stereoacuity was assessed with the subject's refractive correction (if worn). The Preschool Randot measures stereoacuity from 800 to 40 seconds of arc, the Frisby was administered to measure from 400 to 40 seconds of arc and the Titmus circles measure from 800 to 40 seconds of arc. Testing started with the largest disparity and inability to correctly identify the target with the largest disparity was recorded as ‘nil’ stereo. For Preschool Randot and Frisby, a pass on each level was defined as 2 correct responses and for the Titmus circles there was only one target at each level.[17] Testing continued until a level was failed. The stereo threshold was recorded as the smallest disparity correctly identified. It has been suggested that measurable stereopsis should be present for a diagnosis of monofixation to be made, even if only at the level of the Titmus fly (3000 seconds of arc).[6, 18] Nevertheless, we included ‘nil’ stereoacuity as indicating sensory monofixation in intermittent XT since all patients showed motor fusion at near.

Patients

Prevalence of sensory monofixation using different stereotests on a single examination

Forty-four children with intermittent XT (aged 3 to 16, median 6 years) were identified who had all three stereotests (Preschool Randot, Frisby and Titmus) performed at a single examination. If more than one examination with the 3 stereoacuity tests was performed, the earliest examination was included for analysis. For these patients, the median angle of deviation by prism and alternating cover test (PACT) was 20 (range, 12 to 50) prism diopters (pd) at distance and 12pd (range10pd esodeviation to 40pd exodeviation) at near.

Forty-two (95%) of 44 patients had visual acuity of 20/40 or better in each eye; 2 patients had visual acuity of 20/60 in one eye.

Prevalence of sensory monofixation confirmed at a second examination and misclassification of monofixation

Ninety-two children (aged 2 to 17 years), including 37 from the above analysis, met the following criteria: 1) one or more of the 3 stereoacuity tests performed at two sequential examinations, 2) visual acuity normal at each examination (20/40 or better in each eye and ≤ 2 lines of inter-ocular difference) and 3) no treatment between examinations (first time refractive correction, occlusion, exercises, over-minus lenses and surgery). For each stereotest, the first pair of examinations meeting these criteria were included. Seventy-three of 92 patients had consecutive measures using Preschool Randot, 66 using Frisby and 40 using Titmus. Sixty-six (72%) of 92 patients provided data for more than one stereotest, 21 (23%) of whom provided data for all three stereotests, but only 6 (7%) provided data from the same examinations. Patient characteristics (age, angle of deviation, time between examinations) were compared between stereotest groups.

Analyses

Patients were allocated to one of the following three stereoacuity designations for each stereotest at each examination: ‘monofixation’, ‘bifixation’ or ‘uncertain.’ Monofixation: Sensory monofixation was defined as any stereoacuity value worse than the lower 95% confidence interval (lower limit of normal) in age-referenced normal populations.[11, 12] Bifixation: Since there are no clear definitions of bifixation, we performed two separate analyses with two commonly accepted definitions: first at least 40 arc seconds (Table 1) and then at least 60 arc seconds (Table 2). Uncertain: Stereoacuity values worse than the bifixation threshold of 40 or 60 arc seconds but still within the normal range for age (Tables 1 and 2) were classified as ‘uncertain’ because it is not possible to determine whether they represent bifixation or monofixation. The width of the ‘uncertain’ category changes with age because the range of normal stereoacuity values changes with age (Tables 1 and 2).

For the 44 patients with all 3 stereotests measured on a single examination, the rate of monofixation was compared between tests using Fisher's exact test. Agreement between tests was analyzed by comparing proportions classified as monofixation and not monofixation (bifixation combined with uncertain) using McNemars test. Exact 95% Confidence intervals were calculated for each proportion.

Among the patients with stereoacuity testing on two separate examinations, those with subnormal stereoacuity at both examinations were classified as ‘confirmed monofixation’ and those with bifixation at each examination as ‘confirmed bifixation.’ Patients with ‘monofixation’ at the first examination but ‘bifixation’ at the second examination were designated ‘misclassified monofixation.’ Bifixation at the first examination but monofixation at the second examination was defined as ‘possible deterioration.’ Proportions in each category (confirmed monofixation, confirmed bifixation, misclassified monofixation and possible deterioration) were compared between stereotests using Fisher's exact tests. For each stereotest, patients were compared for age, angle of deviation, and time between examinations using General Estimating Equations with contrast statements to account for some patients being included for more than one stereotest.

Results

Prevalence of sensory monofixation using different stereotests on a single examination

With bifixation defined as at least 40 arc seconds, the rate of sensory monofixation was comparable between tests: Preschool Randot 36% (CI 22% to 52%), Titmus 48% (CI 32% to 63%) and Frisby 55% (CI 39% to 70%) (Table 3, P>0.1 for each comparison). When classifying patients as either with or without monofixation, there was good agreement between Titmus and Frisby (P=0.3, Table 4) and Titmus and Preschool Randot (P=0.1, Table 4), but agreement was poorer between Frisby and Preschool Randot (P=0.05, Table 4).

Using a threshold of at least 60 arc seconds to define bifixation, the rate of sensory monofixation was somewhat lower but was again comparable across tests: Preschool Randot 36% (CI 22% to 52%), Titmus 45% (CI 30% to 61%) and Frisby 32% (CI 19% to 48%) (P>0.2 for each comparison). When classifying patients as either with or without monofixation, there was reasonable agreement between Frisby and Titmus (P=0.06), and good agreement between Preschool Randot and Titmus (P=0.2), and Preschool Randot and Frisby (P=0.5).

Prevalence of sensory monofixation confirmed at a second examination and misclassification of monofixation

At both first and second examinations, the median age of patients tested using Titmus was lower than those tested using Preschool Randot or Frisby. (First examination: Titmus 5 years, Preschool Randot 6 years (P=0.03), Frisby 6.5 years (P=0.01); second examination Titmus 6 years, Preschool Randot 7 years (P=0.04), Frisby 7.5 years (P=0.01)). The median time between examinations was comparable between groups: Preschool Randot 6.5 months, Titmus 7.6 months, Frisby 6.9 months (P>0.1 for each comparison).

At the first examination, groups were comparable for median distance angle of deviation by PACT (median 25 pd for each stereotest group; P>0.1 for each comparison) and median near PACT (median 16pd for Preschool Randot and Frisby, 14pd for Titmus; P>0.7 for each comparison). At the second examination, groups were again comparable for median distance PACT (median 20 pd for Preschool Randot and 25pd for Frisby and Titmus; P>0.4 for each comparison) and median near PACT (median 15.5pd for Preschool Randot and 16pd for Frisby and Titmus; P>0.5 for each comparison).

Sensory monofixation confirmed at a second examination

With bifixation defined as at least 40 arc seconds of stereoacuity, the rate of monofixation, confirmed at the second examination, was 21% (CI 12% to 32%) using Preschool Randot, 27% using Frisby (CI 17% to 40%) and 43% using Titmus (CI 27% to 59%) (Table 5). Differences between Preschool Randot and Titmus were statistically significant (P=0.02). With bifixation defined as at least 60 arc seconds, the rate of confirmed monofixation was greater using the Titmus (40%, CI 25% to 57%) compared to both Preschool Randot (21%, CI 12% to 32%; P=0.05) and Frisby (21% CI 12% to 33%; P=0.05).

Misclassified sensory monofixation

With bifixation defined as at least 40 arc seconds, misclassification of monofixation occurred using each of the three stereotests: Preschool Randot 5% (CI 2% to 13%), Titmus 13% (CI 4% to 27%) and Frisby 23% (CI 13% to 35%). The misclassification rate was lower using Preschool Randot than using Frisby (P=0.005, Table 5). When bifixation was defined as at least 60 arc seconds, the rate of misclassification of monofixation was comparable across tests (Preschool Randot 7% (CI 2% to 15%), Titmus 10% (CI 3% to 24%), Frisby 11% (CI 4% to 21%); P>0.5 for each comparison, Table 5).

Discussion

On a single measurement of near stereoacuity in children with intermittent XT, the rate of sensory monofixation ranged from 32% to 55%, depending on the stereotest and the threshold for bifixation. When requiring confirmation at a second examination, the rate was somewhat lower, ranging from 21% to 43%. Misclassification of monofixation by a single stereotest on a single examination ranged from 5% to 23%.

In previous studies, the reported prevalence of reduced stereoacuity in intermittent XT ranges from 11%[19] to 56%,(Sensory outcomes after surgery for intermittent exotropia Morrison D et al. Paper presentation, AAPOS 2009) and depends on the test used, definition of monofixation, and patient age. Even when comparing the same stereotest and the same threshold for bifixation, monofixation rates differ between studies. Using Titmus testing, Baker and Davies reported a prevalence of 23%,[6] whereas Morrison et al found that 56% had reduced or non-detectable stereopsis (Sensory outcomes after surgery for intermittent exotropia Morrison D et al. Paper presentation, AAPOS 2009).The lower rate reported by Baker and Davies may be attributable to their requirement for measurable stereoacuity[6] whereas Morrison et al included patients with no measurable stereoacuity (Sensory outcomes after surgery for intermittent exotropia Morrison D et al. Paper presentation, AAPOS 2009). In our present study, we also included patients with no measurable stereoacuity and, using Titmus and a threshold of at least 60 arc seconds for bifixation, we found a similar rate of monofixation (45%) based on a single measurement. Studies reporting much lower rates of subnormal stereoacuity in intermittent XT include adults,[5, 19] and, therefore, are not directly comparable to our present study.

Previous reports of differences in stereoacuity thresholds between Preschool Randot and Frisby tests[10] suggest that patients often achieve finer thresholds on Frisby testing and therefore, we would have predicted a higher rate of monofixation using the Preschool Randot. Instead, we found the rate of monofixation was similar when tests were compared at a single examination. Interestingly, we found the rate of monofixation to be significantly higher using Titmus than using Preschool Randot or Frisby, when confirmation of monofixation was required at a second examination (Table 5). The higher rate of confirmed monofixation using Titmus may be explained by the younger age of children tested using Titmus compared to those tested using Preschool Randot or Frisby. Nevertheless, we used age-referenced normal population data to account for the possibility of poorer measurable stereoacuity in younger children.

Factors including reduced attention and immaturity in visually normal children result in stereoacuity values that are worse than 40 or 60 arc seconds.[11-15] As illustrated in Tables 1 and 2, normal thresholds can include up to 400 arc seconds using the Preschool Randot[11] and up to 140 arc seconds using Titmus.[12] Since these thresholds cannot be interpreted as representing either bifixation or monofixation, we classified them ‘uncertain.’ The existence of ‘uncertain’ stereoacuity must be considered when interpreting the results of stereo-testing, especially in young children. In this present study the largest proportion of uncertain values occurs using the Preschool Randot (32%) (Tables 1, 2 and Table 3).

We defined misclassification of monofixation as a stereoacuity threshold consistent with monofixation on the first examination followed by a stereoacuity threshold consistent with bifixation on the second examination. Given the current understanding of monofixation, it is unreasonable to propose that conversion of monofixation to bifixation occurs over weeks or months in the natural history of the condition. We found that all three stereotests were prone to misclassify monofixation on a single administration, with rates of misclassification ranging from 5% (Preschool Randot) to 23% (Frisby) (Table 5). We also found that the rate

varied depending on the threshold used to define bifixation (Table 5) because the width of the uncertain category depends on the level of bifixation (Tables 1 and 2). The main reason for misclassification is test-retest variability. Even in non-variable, non-intermittent strabismus, a single octave change is well within test-retest variability for most tests. In addition, we have previously found that variability appears greater in intermittent XT than in other types of strabismus.[8, 9] Serial testing is therefore needed to confirm monofixation by any stereotest, and the optimum number of repeat tests is worthy of further study.

Most studies describing subnormal stereoacuity in intermittent XT define bifoveal fixation as at least 40 or 60 arc seconds. Nevertheless, there are limited data on stereoacuity thresholds in individuals with proven bifoveal fixation because there is no clear standard for bifixation. The best available data are from a study by Parks who defined bifoveal fixation in children using binocular perimetry testing and found average stereoacuity using the Wirt test was 24 arc seconds (range 14 to 40 arc seconds).[18, 20] In more recent studies reporting stereoacuity in intermittent XT, some use this threshold of at least 40 arc seconds to define bifixation,[5, 21] whereas others use a threshold of at least 60 arc seconds to define bifixation.[6, 19](Sensory outcomes after surgery for intermittent exotropia Morrison D et al. Paper presentation, AAPOS 2009). We found that the threshold used to define bifixation can markedly affect the apparent rate of monofixation, particularly with the Frisby test, because 60 arc seconds is subnormal over 3 years of age (Table 3). This controversy also has profound implications for misclassification of monofixation using the Frisby (23% versus 11%, Table 5). The lack of uncertain values using the Frisby, combined with good evidence of reliability,[9, 22, 23] makes the Frisby appealing for establishing the presence or absence of monofixation if the controversy regarding the definition of bifixation can be resolved. New technology such as birefringence scanning[24, 25] may allow for the characterization of a cohort with true bifixation in whom stereoacuity can then be measured and “normal” values redefined.

It has been suggested that, since the majority of patients with intermittent XT demonstrate normal near stereoacuity,[1, 2, 5] intermittent XT with monofixation should be considered a separate clinical entity (monofixational intermittent XT).[7] This raises interesting questions regarding the natural history of intermittent XT. Due to the lack of robust natural history data and the limitations of testing stereoacuity in very young children, it is unclear whether some children with intermittent XT *develop* subnormal stereoacuity and monofixation due to progression of the disease or whether monofixation is an associated primary condition in which bifixation with normal stereoacuity is unobtainable. Natural history data are needed to clarify these issues. Monofixation in intermittent XT may also be important for prognosis and treatment. Some investigators report that pre-operative subnormal near stereoacuity in patients with intermittent XT predicts subnormal near stereoacuity post-operatively,[6, 7, 26] although prospective randomized trials are needed to clarify whether earlier intervention can improve outcomes in such patients.

We found a very low rate of possible deterioration (bifixation first examination monofixation second examination) ranging from 0% to 5% depending on the test used and the threshold used to define bifixation. Our study was not designed to evaluate deterioration and further studies of longer duration are needed. Defining deterioration should also take into account test-retest variability[8, 9] and will almost certainly require multiple measures.

The primary weakness of our study is that, when analyzing change over two examinations, we had somewhat different patient cohorts for each stereotest. Although stereotest groups were comparable for angle of exodeviation, it is possible that other differences between groups (such as age) may have influenced our findings. It is also possible that our reported

rate of monofixation would be different had we used data from other normal populations studies to set our thresholds for normal.

In children with intermittent exotropia, the rate of sensory monofixation differs depending on the stereotest used, the threshold used to define bifixation, and whether or not the findings are confirmed by a second measurement. All three stereotests studied were prone to misclassifying monofixation, ranging from 5% (Preschool Randot) to 23% (Frisby). Robust definitions of monofixation will almost certainly require multiple sequential measurements of stereoacuity and assessment made using single measures should be interpreted with caution.

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Table 1

Near stereoacuity values used to define monofixation and bifixation in children with intermittent exotropia when bifixation was defined as at least 40 arc seconds.

Age (years)	Preschool Randot[11] (arc seconds)			Titmus[12] (arc seconds)			Frisby[12] (arc seconds)		
	Bifoveal	Uncertain	Monofixation	Bifoveal	Uncertain	Monofixation	Bifoveal	Uncertain	Monofixation
3	40	60-400	800-nil	40	50-140	200-nil	40	60	70-nil
4	40	60-200	400-nil	40	50-80	100-nil	40		60-nil
5	40	60-200	400-nil	40	50	60-nil	40		60-nil
6	40	60-100	200-nil	40	50	60-nil	40		60-nil
7	40	60	100-nil	40		50-nil	40		60-nil
8-17	40	60	100-nil	40		50-nil	40		60-nil

Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds; [11, 12] 'uncertain' indicates stereoacuity values worse than 40 arc seconds but still within normal range for age.

Table 2

Near stereoacuity values used to define monofixation and bifixation in children with intermittent exotropia when bifixation was defined as at least 60 arc seconds.

Age (years)	Preschool Randot[11] (seconds of arc)			Titmus[12] (seconds of arc)			Frisby[12] (seconds of arc)	
	Bifoveal	Uncertain	Monofixation	Bifoveal	Uncertain	Monofixation	Bifoveal	Monofixation
3	40-60	100-400	800-nil	40-60	80-140	200-nil	40-60	70-nil
4	40-60	100-200	400-nil	40-60	80	100-nil	40-60	70-nil
5	40-60	100-200	400-nil	40-60		80-nil	40-60	70-nil
6	40-60	100	200-nil	40-60		80-nil	40-60	70-nil
7	40-60		100-nil	40-60		80-nil	40-60	70-nil
8-17	40-60		100-nil	40-60		80-nil	40-60	70-nil

Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds; [11, 12] 'uncertain' indicates stereoacuity values worse than 60 arc seconds but still within normal range for age.

Table 3

Intermittent exotropia patients assessed using three different near stereoacuity tests at a single clinical examination, showing proportions classified as ‘monofixation’, ‘bifixation’ and ‘uncertain.’

Fixation status	Preschool Randot (n=44)		Titmus (n=44)		Frisby (n=44)	
	bifixation ≤40 arcsec	bifixation ≤60 arcsec	bifixation ≤40 arcsec	bifixation ≤60 arcsec	bifixation ≤40 arcsec	bifixation ≤60 arcsec
Monofixation	36%[a]	36%[a]	48%[a]	45%[a]	55%[a]	32%[a]
Bifixation	32%	50%	43%	48%	45%	68%
Uncertain	32%	14%	9%	7%	None	None

Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds[11, 12], ‘bifixation’ was defined as at least 40 arc seconds or at least 60 arc seconds and ‘uncertain’ was defined as worse than 40 or 60 arc seconds but within normal range for age.

[a]The rate of monofixation was comparable across tests using a threshold of at least_40 arc seconds for bifixation (P>0.1 for each comparison) and using a threshold of at least 60 arc seconds for bifixation (P>0.2 for each comparison).

Table 4

Agreement between stereoacuity testing methods when classifying individual children with intermittent exotropia (n=44) as ‘monofixation’ or ‘not monofixation.’

Stereotest used	Titmus		Frisby	
Frisby	Monofixation: 41%	P=0.3		
	Not monofixation: 39%			
Preschool Randot	Monofixation: 30%	P=0.1	Monofixation: 27%	P=0.05
	Not monofixation: 45%		Not monofixation: 36%	

Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds. [11, 12] ‘Not monofixation’ was defined as stereoacuity within age-referenced normal thresholds (bifixation defined as at least 40 arc seconds).

Table 5

Classification of monofixation and bifixation at consecutive examinations in children with intermittent exotropia

	Preschool Randot (N=73)		Titmus (N=40)		Frisby (N=66)	
	Bifixation ≤40 secs	**Bifixation ≤60 secs**	**Bifixation ≤40 secs**	**Bifixation ≤60 secs**	**Bifixation ≤40 secs**	**Bifixation ≤60 secs**
Confirmed monofixation	21%[a]	21%[c]	42.5%[a]	40%[c]	27%	21%[c]
Confirmed bifixation	30%	47%	17.5%	28%	42%	65%
Misclassified monofixation	5%[b]	7%	12.5%	10%	23%[b]	11%
Possible deterioration	0%	1%	2.5%	5%	2%	3%
Uncertain (either examination)	44%	25%	25%	17%	6%	0%

Confirmed Monofixation was defined as stereoacuity worse than previously published age-referenced normal thresholds[11, 12] at both examinations; 'misclassified monofixation' was defined as stereoacuity subnormal for age on first examination and bifixation (at least 40 arc seconds or at least 60 arc seconds) on second examination; 'Possible deterioration' was defined as bifixation on the first examination and monofixation on second examination.

[a] the rate of confirmed monofixation was significantly higher using Titmus compared to Preschool Randot (P=0.02)

[b] misclassification of monofixation occurred significantly less using Preschool Randot compared to Frisby (P=0.005)

[c] the rate of confirmed monofixation was significantly higher using Titmus compared to Preschool Randot and Frisby (P<0.05 for each comparison)