Increasing incidence and risk factors for divergence insufficiency esotropia

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PURPOSE To document the increasing incidence of divergence insufficiency (DI) esotropia and to identify risk factors for DI.

METHODS All patients with a diagnosis of esotropia seen by one provider (DLG) over 41 years were identified from the medical record. Patients with onset of strabismus before age 10 years or with prior strabismus surgery were excluded. Cases of esotropia associated with thyroid eye disease, scleral buckles, trauma, neurological diseases, or atypical misalignment were included but not labeled as DI regardless of the distance versus near deviation. The remaining patients, whatever the original diagnosis, were retrospectively categorized as having, or not having, DI, using a uniform criterion: distance esotropia $\geq 5^{\Delta}$ more than near esotropia.

RESULTS The percentage of DI patients among acquired esotropia patients increased significantly between the first and second half of the 41-year period, from 11.8% to 29.4% ($P < 0.001$). Multivariate logistic regression identified advancing age and the use of progressive addition lenses as risk factors for the development of DI.

CONCLUSIONS The incidence of DI is increasing. DI's association with age and progressive addition lenses may help us to understand its etiology and to decrease the prevalence of this condition in the future. (J AAPOS 2021;25:278.e1-6)

Primary divergence insufficiency (DI) is a gradually progressive esotropia that is greater at distance fixation than at near. This acquired strabismus pattern is deemed by Jacobson[1] as well as by Repka and Downing[2] to be distinct from those due to neurological lesions. A previous study reported an increase in the incidence of DI in recent years.[2] However, DI cases in that study were identified by International Classification of Diseases (ICD) codes for divergence insufficiency. Because DI may not have been recognized as frequently in the past, it is possible that many cases in earlier years that should have been coded as DI may have been coded instead using more routine esotropia codes or even mistaken for abducens nerve palsy/paresis. In addition, some series of DI patients focused only on those referred for surgical intervention.[2,3] The primary purpose of the current study was to determine more accurately the incidence of DI by reviewing the medical records of all patients with acquired esotropia seen by one provider over 41 years, reclassifying/rediagnosing them as DI or not, using a uniform criterion. The pathogenesis of DI is still under active investigation, with multiple theories proposed.[4] A secondary purpose of this study was to identify risk factors for developing DI, in the hope of better understanding potential mechanisms underlying this disease.

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Subjects and Methods

The Johns Hopkins Medicine Institutional Review Board approved this study, which was compliant with the US Health Insurance Portability and Accountability Act of 1996. To identify patients with acquired esotropia, our internal database, the Wilmer Information System[5] was searched for patients with ICD-9 codes of 378.0* (esotropia—all types) and 378.85 (divergence insufficiency) seen between January 1978 and April 2013 by one major provider (DLG) in our Pediatric Ophthalmology and Adult Strabismus Division. Our institution adopted the Epic electronic medical record system in spring 2013. The Epic database was searched for patients with ICD-9 and ICD-10 codes of 378.0*and H50.0* (esotropia—all types), and 378.85 and H51.8 (divergence insufficiency), seen by the same provider between May 2013 and December 2018. The medical records of all identified patients were retrospectively reviewed.

Inclusion criteria for the list of acquired esotropia patients were onset of esotropia at age ≥10 years and presentation with esotropia at the first visit. Patients were excluded entirely if they had a prior history of strabismus surgery. Deviations were measured by prism and alternating cover testing with the patient's habitually worn glasses in place. Measurements were adjusted for any prism worn. Additional data collected included sex, initial visit date, age at presentation (measured in years), best judgement of years of age at onset of double vision or eye misalignment (whichever was noted first), and type of reading add if any.

To identify as homogenous a population of DI patients as possible, for the purpose of considering likely etiologies, we segregated out conditions that could possibly cause a distance-versus-near esotropia pattern mimicking DI. Specifically, these were patients with a history of thyroid eye disease, scleral buckling surgery, trauma causing eye misalignment, or neurological disorders such as cerebellar degeneration, ocular myasthenia gravis, multiple sclerosis, intracranial tumor, and stroke causing acute-onset trochlear or abducens nerve palsy. We included these patients in our group of acquired esotropia patients, but we did not categorize them as having DI, regardless of the distance versus near measurements. In addition, we segregated out patients with atypical misalignment patterns that could be hints of outlier etiologies for the acquired esotropia, such as abduction limitation > -1 ($0 =$ full abduction; $-4 =$ no abduction beyond midline), lateral incomitance between right and left gazes $\geq 6^{\Delta}$, A or V pattern $\geq 7^{\Delta}$, or vertical deviation straight ahead $\geq 4^{\Delta}$. We analyzed the distance esotropia versus near esotropia for these atypical misalignment patients, but we did not categorize any of these as having DI, regardless of the distance versus near measurements. We recorded gazes in the cardinal directions for all patients and excluded mild abducens nerve paresis from categorization as DI based on horizontal incomitance $\geq 6^{\Delta}$ or abduction limitation > -1, if there were not already any clear neurological or traumatic causes.

The remaining acquired esotropia patients were reclassified as having DI or not using a uniform criterion: distance esotropia $\geq 5^{\Delta}$ more than near esotropia.[2,6,7]

All data were analyzed using R-3.6.2 (http://www.R-project.org/). Because of many patients' uncertainty regarding timing of symptom onset, we elected to report our tabulations of percentages of DI among acquired ET patients relative to the initial visit date. We did process the data relative to the reported year of symptom onset and found essentially the same distributions of data, though with slightly more scatter.

Plots of percentages of acquired ET patients were fitted with quadratic models. Locally estimated scatterplot smoothing curves were added in the plot of percentage of esotropia patients with DI or neuromuscular diseases to show the trend of data. Continuous variables were compared using Wilcoxon rank-sum tests. The χ^2 test of homogeneity was used to compare the use of progressive addition lenses (PALs) between DI patients and non-DI patients. Multivariate logistic regression was used to model the probability of DI versus other forms of acquired ET. The main predictor was PAL use (yes/no). The covariates were chosen based on our hypotheses that demographic information (age and sex) and year could affect the probability of a patient developing DI.

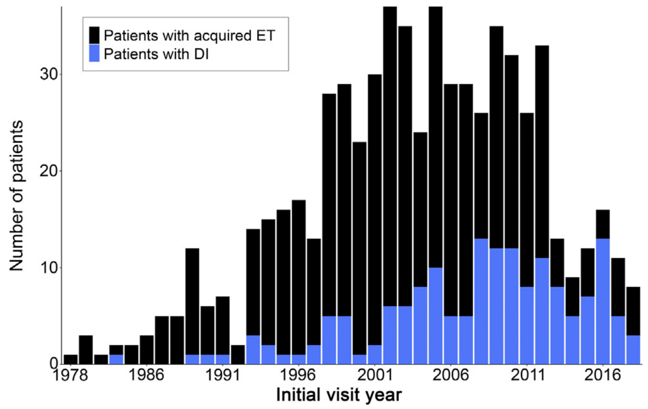

FIG 1. Number of acquired esotropia (ET) patients showing the proportion who had divergence insufficiency (DI), who presented in each year from 1978 through 2018.

Results

A total of 646 acquired esotropia patients were included in our study. Figure 1 shows the number of patients each year. Table 1 shows the characteristics of patients who were included but not categorized as having DI regardless of the distance versus near deviations. Of all the patients with any of the bottom four misalignment patterns that may be hints of outlier etiologies for the acquired esotropia, only 14 of them had a DI pattern (2.2% of the 646 patients). The 256 patients described in Table 1 were analyzed as cases of acquired esotropia without DI.

The remaining 390 patients were classified as having, or not having, DI based on the comparison of distance and near deviations. In the period 1978-1998, 11.8% of the acquired esotropia patients presented with DI, whereas in the period 1999-2018, 29.4% of the acquired esotropia patients presented with DI ($P < 0.001$). The quadratic model (Figure 2) with a moderately strong goodness of fit ($R^2 = 0.647$) demonstrates an accelerating (nonlinear) increase in the percentage of acquired esotropia patients with DI over time. Figure 3 shows that within each 10-year age group, the percentage of acquired esotropia patients with DI increased from the first 21 years to the second 20 years, except in the age range of 70-80 years.

Figure 4 shows the number of DI and acquired esotropia patients in each presenting age group. With increasing age, a larger proportion of acquired esotropia patients had DI until the curve started to trend downward at around 75 years of age (Figure 5). Also shown in Figure 5 is the percentage of acquired esotropia patients with neurological disorders, which did not increase appreciably with age.

Seventeen of the patients with DI (10.4%) presented before age 40 years. The time from reported symptom onset to initial clinic visit was longer for DI patients than for other esotropia patients (8 ± 12 vs 5 ± 8 years; $P < 0.001$).

The average near and distance deviations of DI patients were $6.9^{\Delta} \pm 9.5^{\Delta}$ and $15.9^{\Delta} \pm 10.3^{\Delta}$, with an average difference of $9.0^{\Delta} \pm 4.1^{\Delta}$.

Table 1. Additional characteristics of patients among the entire 646 with acquired esotropia who were included in the study but, because of these characteristics, were not categorized as having divergence insufficiency regardless of the distance versus near measurements[a]

Characteristics	No. (%)
Thyroid eye disease	19 (2.9)
History of scleral buckle surgery	46 (7.1)
Trauma causing eye misalignment	67 (10.4)
Neurologic disorders[b]	54 (8.4)
Abduction limitation > −1	26 (4.0)
Lateral incomitance ≥6 PD	11 (1.7)
V pattern ≥7 PD	7 (1.1)
Vertical deviation straight ahead ≥4 PD	26 (4.0)
Total not categorized	256 (39.6)
Total in study	646 (100)

PD, prism diopters.
[a]Patients with more than one of these conditions were included only in the first category where they qualified, from the top down.
[b]Including cerebellar degeneration, supranuclear palsy, ocular myasthenia gravis, multiple sclerosis, intracranial tumor, and stroke.

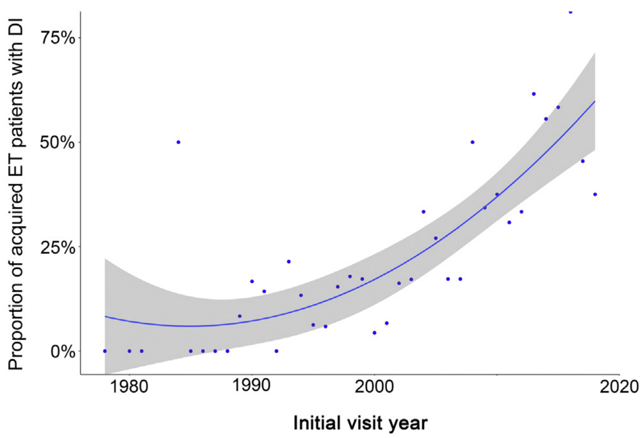

FIG 2. Proportion of acquired ET patients with DI plotted versus initial visit year. A quadratic model was fitted: predicted % acquired ET patients with DI (in decimal form) = 1939 − 1.954*(visit year) + 4.921e-04* (visit year)^2. (F[2,35] = 32.06; P = 1.225e-08; R^2 = 0.647). The shaded area represents the 95% confidence interval (there is a 95% probability that the true regression line of the population will lie within the confidence interval of the regression line calculated from the sample data).

eFigure 1 (available at jaapos.org) shows that only a small number of acquired esotropia patients had large vertical deviations, most of whom were already excluded from the classification of DI based on other criteria listed in the Methods. The average vertical deviation of DI patients was $0.0^{\Delta} \pm 0.9^{\Delta}$ (eFigure 2, available at jaapos.org).

In the period 1978-1998, 5.3% of acquired esotropia patients were wearing PALs, whereas in the period 1999-2018, 16.8% of the acquired esotropia patients were using PALs ($P < 0.001$). The quadratic model (Figure 6) with a moderately strong goodness of fit (R^2 = 0.619) demonstrates that the rate of increase in the percentage of acquired esotropia patients wearing PALs has been nonlinear as well, similar to the increase in the percentage of acquired esotropia patients with DI. DI patients were more likely to wear PALs than non-DI patients (22.1% vs 11.4%; $P < 0.001$; Table 2).

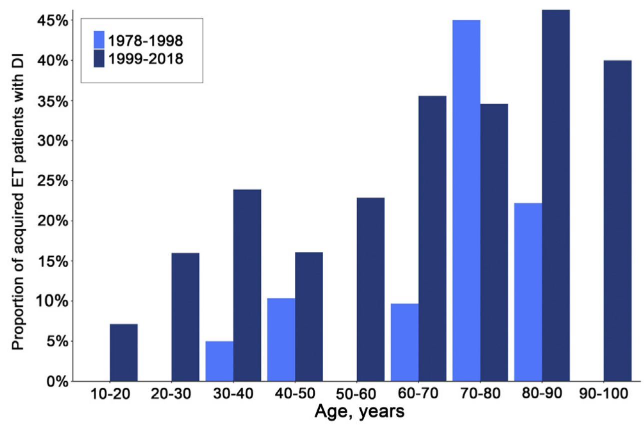

FIG 3. Proportion of acquired ET patients with DI in each 10-year age group in the first 21 years versus the second 20 years in the study period.

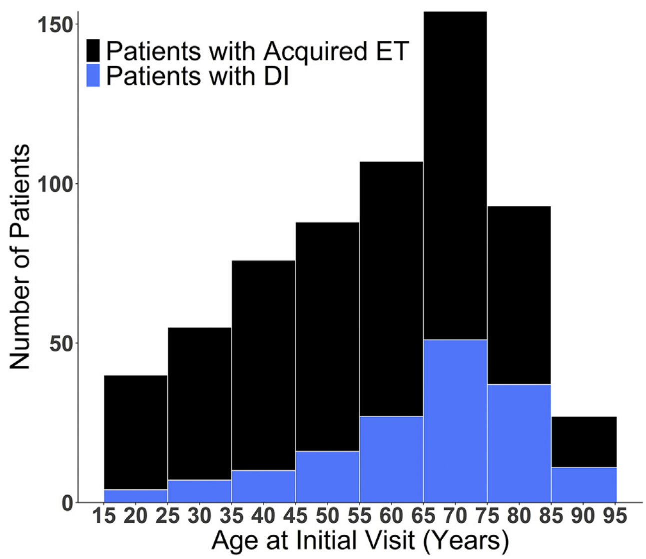

FIG 4. Number of acquired ET patients showing the proportion who had DI in each age group.

Table 3 shows logistic regression results. Regardless of age or year, patients wearing PALs had increased odds of having DI (OR = 2.09; 95% CI, 1.29-3.36). DI was also more common among older patients (OR = 1.02; 95% CI, 1.01-1.03).

Discussion

Our study suggests that the incidence of DI has increased significantly from 1978 to 2018 in our single provider's practice. The increase in DI over the 41-year period still

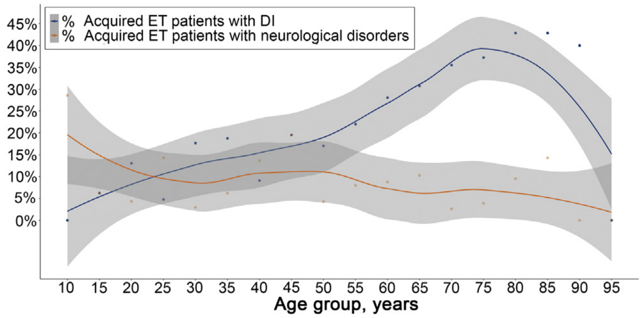

FIG 5. Percentage of acquired ET patients with DI and percentage of acquired ET patients with neurological disorders plotted versus age at presentation (5-year age groups). Locally estimated scatterplot smoothing was used to help see the trend of the data points. The shaded areas represent the 95% confidence interval (there is a 95% probability that the true regression line of the population will lie within the confidence interval of the fitted line for the sample data). The last data points of the two curves coincided.

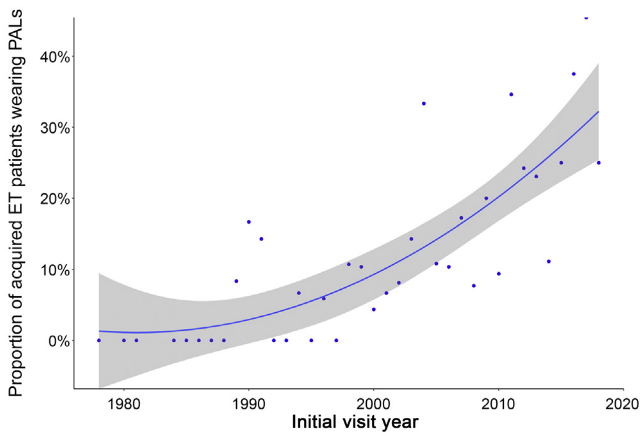

FIG 6. Proportion of patients with acquired esotropia wearing progressive addition lenses (PALs) plotted versus initial visit year. A quadratic model was fitted: predicted % acquired ET patients wearing PALs (in decimal) = 895.20 − 0.90*(visit year) + 2.28e-04*(visit year)^2 ($F[2,35] = 31.11$; $P = 1.718e\text{-}08$; $R^2 = 0.619$). The shaded area represents the 95% confidence interval (there is a 95% probability that the true regression line of the population will lie within the confidence interval of the regression line calculated from the sample data).

holds true when the patients are stratified by age, so it is not attributable to potential changes in the age distribution of the provider's patient population over time. The strength of our study lies in the use of a uniform DI criterion to classify all acquired esotropia patients presenting to the practice. This approach eliminates physician bias in diagnosis coding and includes more DI patients than those who required surgery. We did not classify any acquired esotropia patient as having DI if the misalignment was caused by conditions that might suggest outlier etiologies so that our population of patients with DI would be as pure as possible.

Table 2. Progressive addition lenses are associated with divergence insufficiency (DI) esotropia (χ^2 test of homogeneity; *P* value of <0.001)

Use of progressive addition lenses	DI, no. (%)	Acquired ET, non-DI, no. (%)
Yes	36 (22.1)	55 (11.4)
No	127 (77.9)	428 (88.6)

A noteworthy finding of our study was the delay from symptom onset to diagnosis for DI patients compared with other esotropia patients, highlighting the insidious nature of DI. This is probably related to the slow onset and progression of the distance double vision in DI patients who are still able to see perfectly well at near for many years and do not seek help as soon as other acquired esotropia patients, who often see double at both distance and near from early in the course.

Several hypotheses have been proposed regarding the etiology of DI. One theory is the "sagging eye syndrome" (SES), which proposes that age-related degeneration of orbital connective tissues can lead to downward displacement of the fascial "pulley" of the lateral rectus muscles and weaken abduction.[8] While this mechanism undoubtedly exists, it does not explain the increasing incidence of DI, controlled for age, that we have documented over the past 41 years. Another theory, proposed by Guyton, postulates that near work, without sufficient spectacle lens power for comfortable near focusing, leads to chronic activation of the near triad, which can cause an unwanted increase in convergence tonus.[9] Over time, in response to this chronic vergence tonus, medial rectus muscles lose sarcomeres and shorten, via the phenomenon of misguided muscle length adaptation,[10,11] whereas lateral rectus muscles gain sarcomeres and elongate in response to stretch and decreased stimulation, leading to the characteristic pattern of DI. Indeed, Bothun and Archer[12] reported tightness of medial rectus muscles in patients undergoing surgery for DI, and Chaudhuri and Demer[8] noted lateral rectus muscles to be significantly more lengthened than medial rectus muscles in DI patients. A similar mechanism is seen in esotropia associated with undercorrected early presbyopia.[13]

Our study found the use of PALs to be a risk factor for DI after controlling for age. Increases in PAL use may at least partly explain the increase in the incidence of DI. PALs can compensate for the loss of accommodation in presbyopia but not if patients do not look down far enough to utilize enough of the power of the progressive adds.[14] This is particularly applicable when individuals work on the computer with general-purpose PALs in which clear near vision is limited to the lowest areas of gaze. In fact, it has been reported that general-purpose PAL users adopt more elevated head posture during computer work than those wearing single vision lenses.[15] Because properly using PALs compared with other types of reading glasses requires looking farther into downgaze, it is not surprising

Table 3. Multiple logistic regression analysis of factors associated with having divergence insufficiency esotropia versus other forms of acquired esotropia[a]

Study parameter	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Sex	0.85 (0.59-1.22)	0.371	0.92 (0.63-1.34)	0.674
Progressive add lens use	2.21 (1.38-3.50)	<0.001	2.09 (1.29-3.36)	0.002
Year of initial visit	1.01 (1.00-1.03)	0.106	1.00 (0.98-1.02)	0.745

CI, confidence interval; *OR*, odds ratio.
[a]The equation employed in the multivariate logistic regression is Logit(DI) = 3.880 + (0.019*age) − (0.080*sex) + (0.739*PAL use) − (0.003*year). Sex as categorical variable: "1" if female, "2" if male; PAL use as categorical variable: "1" if using, "0" if not using. Hosmer-Lemeshow goodness of fit test for our multivariate model showed $\chi^2 = 2.63$, df = 8, $P = 0.955$. Our model fit well because there was no significant difference between the model and the observed data ($P > 0.05$).

that many PAL wearers may not use the full power of their progressive addition segments when viewing close objects. The resulting uncompensated need for accommodation can increase convergence tonus and shorten medial rectus muscles relative to lateral rectus muscles over time, contributing to the development of DI. The esotropia does not manifest as much at near because near viewing requires convergence of the eyes, and the relatively shorter medial rectus muscles simply lessen the amount of convergence needed. We therefore recommend that PAL wearers be educated on the proper way to use these readings adds (looking through the bottom-most part of the lenses for near work) and use "computer" bifocals or "computer" PALs instead of general-purpose PALs for computer work.

Our multivariate regression model also demonstrates a significant association of age with risk of DI being the cause of acquired esotropia. Figure 5 shows that the percentage of acquired esotropia patients who had DI peaked around age 75 for age at initial clinic presentation and then decreased. We hypothesize that patients with undercorrected presbyopia will attempt to add whatever residual accommodation they can muster to see better up close, which leads to chronically increased convergence tonus, leading to DI.[9] Around age 60-65, however, the loss of accommodation with age is complete,[16] and the improvement in vision from attempted accommodation diminishes to essentially zero. If the loss of accommodation with age, with incomplete compensation by PALs, is a factor contributing to the development of DI, that effect should be essentially over around age 60-65. When we factor in the delay from symptom onset to clinic presentation, this may help explain the lack of further increase in the percentage of DI among acquired esotropia patients at older ages. This lower percentage in the oldest age groups is not attributable to an increased incidence of acquired esotropia from neurological disorders with age, because the percentage of acquired esotropia patients with neurological disorders did not increase significantly with age in the study.

In SES, the culprit is considered to be age-related degeneration of orbital connective tissues.[8] If the involution of orbital connective tissues were the only mechanism for DI, however, we would expect the degenerative process to continue with every year that the person is alive, resulting in a continued increase in the risk of DI throughout a person's life.[17] It would be hard to explain the lack of further increase in the percentage of DI among acquired esotropia patients in the oldest age groups solely on the basis of SES. Additional mechanisms likely contribute to causing DI.

Recent data by Goseki and colleagues[18] showed that the percentage of SES among all diplopia patients increased until even 90 years of age. However, that study was limited by the low number of SES cases and other causes of diplopia over age 90. Moreover, age-related distance esotropia was a subpopulation (35%) of SES in that study (an assumption that was not confirmed with magnetic resonance imaging), and the authors did not specifically separate this population from the other types of SES when calculating the incidence with age. It is uncertain whether the incidence of divergence insufficiency per se increased at older ages. We believe that our study better represents the incidence of primary divergence insufficiency relative to other causes of acquired esotropia.

Of interest in our study were patients under age 40 who developed DI. Two recent studies have demonstrated that DI in young adults is associated with prolonged near work.[7,19] In a prospective study in young DI patients, refraining from excessive near work decreased their degree of esotropia.[19] This mechanism of DI in young adults points to the dynamic adaptation of horizontal rectus muscle length. Near work demands a larger accommodative effort with associated increased convergence tonus that can shorten medial rectus muscles relative to lateral rectus muscles over time. The requirement for near vision has increased over the years of the study period, with the proliferation of computers, smart phones, and tablets, which often have smaller print sizes and lower contrast than printed material.[20] The development of DI due to excessive near work may contribute to increasing incidence of DI at all ages.

Our study was limited, first, by its retrospective nature. Second, diagnoses of neurological diseases were made through history, and neuroimaging was only performed at clinician discretion. However, follow-up monitoring of the DI patients revealed no related neurologic findings. Third, high myopia was not an exclusion criterion for DI, although no patient with DI was found to have myopia of ≥10 D. Fourth, there could be a possible referral bias.

However, we know of no reason why DI patients should be referred disproportionately more often than other acquired esotropia patients, especially within a given age range.

In conclusion, the incidence of DI has increased over a recent 41-year period. PAL use and older age at clinic presentation (up until about age 75 years) were associated with increased risk of DI. These findings, combined with the occurrence of DI in young patients engaging in prolonged near work, support the concept that chronically increased convergence tonus, with subsequent shortening of medial rectus muscles relative to lateral rectus muscles, can be one of the mechanisms contributing to the etiology and/or evolution of many cases of DI.

Acknowledgments

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