Feasibility and Comparison of Visual Acuity Testing Methods in Children with Neurofibromatosis Type 1 and/or Optic Pathway Gliomas

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Purpose. Longitudinal ophthalmologic clinical trials in young children require multiple visual acuity (VA) testing methods—especially when the subjects have cognitive and developmental delay. This study evaluated the success rate and comparability of two different VA testing methods in children with neurofibromatosis type 1 (NF1) and/or optic pathway gliomas (OPGs).

Methods. Two institutions prospectively enrolled children 10 years or younger with NF1 and/or an OPG. Both Teller grating acuity (TAC) and recognition acuity using the computerized version of the Amblyopia Treatment Study VA testing protocol that limits responses to four letters (H, O, T, or V) were attempted in all subjects. The association of age and diagnosis of NF1 on success rate was analyzed. Differences in grating and recognition acuity were compared.

Results. One hundred twenty-seven children met inclusion criteria (median age = 5.58 years). Of 127 subjects, 11 (8.7%) could not complete monocular TAC testing in either eye; 39 (30.7%) could not complete HOTV testing and were younger than those able to complete HOTV testing (mean = 2.9 vs. 7.0 years, respectively; $Z = -8.3$, $P < 0.01$). Older age was associated with successful HOTV testing and remained significant in all regression analyses ($P < 0.01$). The within-subject logMAR values for TAC and HOTV testing results were significantly correlated ($r = 0.69$, $P < 0.01$).

Conclusions. Young children with NF1 and/or OPGs were frequently unable to complete recognition acuity testing. These factors are important to consider when designing a clinical trial for children with NF1 and/or OPGs. (*Invest Ophthalmol Vis Sci.* 2013;54:1034–1038) DOI:10.1167/iovs.12-11385

Standardized visual acuity (VA) testing and outcome measures are well established for clinical trials of ophthalmologic disease in adults.[1,2] However, ophthalmologic clinical trials in young children may require different VA testing methods due to the patient's age and developmental abilities. The early treatment of diabetic retinopathy study (ETDRS) chart and computer-based ETDRS testing algorithms have been used in pediatric studies enrolling children who were 7 years old and who could recognize most letters of the alphabet.[3,4] For younger children (i.e., <6 years) who were able to recognize some, but not all, letters of the alphabet, a computerized version of the Amblyopia Treatment Study VA protocol limits responses to four different optotypes (i.e., H, O, T, V; hereafter referred to as "computer-based HOTV") with crowding bars. The computer-based HOTV protocol has been used in children as young as 2 years, although less than half of the healthy children younger than 3 years old could complete the testing.[5–7] Using a preferential looking paradigm, Teller acuity cards (TAC) can measure grating acuity in preverbal and preliterate children as young as 6 months old with a variety of eye conditions.[8–14] Both the computer-based HOTV and TAC methods are performed according to a standardized protocol and report the results in logMAR, which is ideal for statistical analysis; and they have been incorporated into longitudinal studies for a variety of eye diseases.[5,12,15]

The analysis of VA as a primary outcome in either cross-sectional or longitudinal pediatric ophthalmologic studies can be problematic since subjects of the same age may not be able to complete the same VA test. Longitudinal studies are further complicated by same-aged subjects transitioning between testing methods at different points in the study. Additionally, the VA results produced by ETDRS charts, computer-based HOTV, and TAC were not equivalent, thereby complicating the analysis and interpretation of both short-term and long-term results.[8,11,16,17] Young children's ability to cooperate and provide a reliable VA result may also be significantly associated with their comorbid medical conditions (e.g., attention-deficit disorder [ADD], side effects of treatment) and intellectual disability.

Children with optic pathway gliomas (OGPs), low-grade gliomas involving the proximal afferent visual system, are a good example of a heterogeneous group of patients that require frequent and long-term monitoring for visual loss. Children with OPGs secondary to neurofibromatosis type 1 (NF1) and sporadic OPGs (i.e., not related to NF1) are at most risk for vision loss between 18 months and 8 years of age, although it can occur into the teenage years.[18–21] Based on our experience, inability to complete age-appropriate VA tests is most pronounced in children with NF1, who frequently have developmental delay and ADD.[22,23] Unfortunately, none of the pediatric OPG clinical trials have used a standardized VA testing protocol to measure treatment efficacy. An ideal VA testing protocol for an OPG clinical trial would need to consider the patient-specific factors (i.e., developmental delay and ADD) that may be associated with success in completing VA testing, while allowing inclusion of the widest range of patient ages.[24] To address this issue, we describe the success rate and comparability of TAC and HOTV testing in children with NF1 and/or OPG.

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Methods

Patients

Children 10 years and younger being examined for their routine eye examination at Children's National Medical Center and the Hospital for Sick Children between January 1, 2012, and June 30, 2012, were included if they met formal criteria for NF1 (with or without a known OPG) or had sporadic OPG determined by biopsy or radiographic features. Those subjects meeting inclusion criteria had the following data abstracted from their clinical chart onto a standardized data form: age, sex, race, diagnosis, OPG location, success and results of TAC and HOTV testing, color vision, optic nerve appearance, and visual field results. All ophthalmologic data were prospectively collected at the time of the visit. The research followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Data abstracted onto the study document did not collect any protected health information or identifying information.

VA Testing Protocols

All subjects underwent monocular VA testing using both TAC and computer-based HOTV testing. The neuro-ophthalmologist (RAA or AR) or one dedicated orthoptist/research coordinator from each site performed all of the vision testing as part of the patient's scheduled clinical visit. All examiners were experienced in using both the TAC and HOTV protocols in children. TAC was performed according to the previously published protocol in a well-illuminated exam room, but without the use of testing stage.[15] The TAC testing distance was maintained at 55 cm for all subjects. If the patient was uncooperative during the visit, breaks were permitted and testing was reattempted. The examiner could choose to stop TAC testing in subjects who, despite multiple testing attempts and breaks, would not cooperate with testing due to fatigue, irritability, or anxiety. Subjects unable to reliably complete testing or those who remained uncooperative despite permitted breaks were labeled as "untestable." Since obtaining VA is an essential component to their clinical care, every effort was made to complete VA testing. TAC results were recorded as cycles/cm and were converted to logMAR. The computer-based HOTV testing was performed identically to the Amblyopia Treatment Study (ATS) procotol.[5,25] Testing was performed in a dimly lit room, and subjects were asked to correctly identify each H, O, T, V optotype presented separately, by either verbally naming the letter or pointing to the letter on a lap card. If the subject was not able to correctly identify each letter or match the largest letter on the screen to the lap card in the setting of normal vision, they were determined to be "untestable." Subjects with severe VA loss (e.g., counting fingers, no light perception) who could complete TAC or HOTV testing with the fellow eye were considered "testable" as their vision, not their ability to complete the testing, precluded them from completing the task.

Statistical Analysis

Demographic and clinical characteristics were summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as sex). The Wilcoxon rank-sum test was used to compare the ages between groups success in completing the HOTV testing. The χ^2 test was used to determine the between group differences by diagnosis for testing success. Logistic regression analysis examined the individual (i.e., unadjusted analysis) and combined (i.e., adjusted analysis) association of age, center, and diagnosis (NF1 versus non-NF1) on testing success. Spearman's rank correlation and linear regression analysis determined the relationship between TAC and HOTV scores for the children who could complete both tests. To account for the intereye correlation, a generalized estimating equation was employed.

Results

One hundred and twenty-seven children were evaluated (median age = 5.58 years, range 0.58–10.72 years); 74 subjects were from one site and 53 from the other. Table 1 lists the clinical characteristics of the subjects.

Of 127 subjects, 11 (8.7%) could not complete monocular TAC of both eyes (see Table 2), 8 (6.3%) could not complete testing in either eye, and 3 (2.4%) could complete testing in only one of the seeing eyes. Age and diagnosis (NF1 versus non-NF1) were significantly associated with the success of TAC testing in both the unadjusted and adjusted regression analyses ($P < 0.01$, $P < 0.02$, respectively). Children with NF1 who were able to complete TAC testing were slightly younger (median = 5.7 years) than children without NF1 (median = 6.6 years). Of 103 children with NF1, 6 (5.8%) could not complete TAC and were of similar age (median = 2.4 years) to the 5 (20.8%) of 24 children without NF1 who failed to complete TAC testing.

Of 127 subjects, 39 (30.7%) could not complete HOTV testing with either eye and were younger (mean = 2.9 ± 1.2 years) compared to those able to complete HOTV testing (mean = 7.0 ± 2.1 years; $Z = -8.3$, $P < 0.01$; see Fig. 1). In both Pearson χ^2 ($P = 0.97$) and the unadjusted and adjusted regression analyses, diagnosis (NF1 versus non-NF1) was not associated with success of HOTV testing ($P = 0.82$, $P = 0.72$, respectively). Age was significantly associated with success of HOTV testing in both unadjusted and adjusted regression analyses ($R^2 = 0.62$, $P < 0.01$, $R^2 = 0.62$, $P < 0.01$). Study center was associated with success of HOTV testing in the unadjusted regression analysis ($R^2 = 0.05$, $P < 0.01$) but did not reach significance in the adjusted regression analysis ($P = 0.20$), due to the lower subject age (5.1 vs. 6.6 years) of one center compared to the other. A post hoc regression analysis

Table 1. Clinical Characteristics

	Study Subjects, $N = 127$
Age, mean/median (range)	5.7/5.5 (0.58–10.42)
Distribution, No. (%)	
<2.0	9 (7.0)
<3.0	20 (15.7)
<4.0	34 (26.8)
<5.0	55 (43.3)
<6.0	68 (53.5)
<7.0	86 (67.7)
<8.0	100 (78.7)
<9.0	105 (82.7)
<10.0	119 (93.7)
<11.0	127 (100)
Female sex, No. (%)	68 (53.5)
Race, No. (%)	
White/Caucasian	102 (80.3)
Black/African American	8 (6.3)
Asian	11 (8.7)
Multiple races	6 (4.7)
Ethnicity, No. (%)	
Non-Hispanic	117 (92.1)
Hispanic	10 (7.9)
Diagnosis, No. (%)	
NF1 with optic pathway glioma	68 (53.5)
NF1 without optic pathway glioma	35 (27.6)
Sporadic optic pathway glioma	24 (18.9)

Ages are expressed in years.

Table 2. Success of Teller Acuity Card and Computer-Based HOTV Testing by Age Group

Age Group, y	TAC Success, *N* (%)	HOTV Success, *N* (%)
0.0–1.9	5/9 (56)	0/9 (0)
2.0–2.9	9/11 (82)	0/11 (0)
3.0–3.9	10/14 (71)	3/14 (21)
4.0–4.9	21/21 (100)	15/21 (71)
5.0–5.9	13/13 (100)	13/13 (100)
6.0–6.9	17/18 (94)	16/18 (89)
7.0–7.9	14/14 (100)	14/14 (100)
8.0–8.9	5/5 (100)	5/5 (100)
9.0–9.9	14/14 (100)	14/14 (100)
10.0–10.9	8/8 (100)	8/8 (100)

determined that TAC VA (logMAR) was not significantly associated with the success rate of HOTV testing ($P = 0.61$). Children with NF1 who were able to complete HOTV testing were of similar age (median = 6.8 years) to children without NF1 (median 6.7 years). Of 103 children with NF1, 31 (30.1%) could not complete HOTV and were slightly younger (median = 2.7 years) than the 8 (33.3%) of 24 children without NF1 who failed to complete HOTV testing.

The within-subject logMAR values for TAC and HOTV testing results were significantly correlated (Spearman's $r = 0.69$, $P < 0.01$). The adjusted coefficient of determination (adjusted $R^2 = 0.67$) from the linear regression analysis indicates that 67% of the variability in the HOTV results can be explained by the TAC results. The addition of age and diagnosis to the regression model did not significantly increase the proportion of variance (<1.5%, respectively). A Bland-Altman plot demonstrates the agreement between TAC and HOTV testing (see Fig. 2).

Discussion

This study describes TAC and HOTV testing in a patient population known to have comorbid medical conditions (i.e., attention deficit–hyperactivity disorder [ADHD]) and developmental delay that could affect both the success rate of their testing as well as the relationship between grating and recognition acuity. A relatively small portion of the population (8.7%) could not complete monocular TAC testing for both eyes. Nearly one-third of our subjects could not complete HOTV testing, most of whom were younger than 5 years old. The relatively high rate of HOTV failure highlights both the association of age on testing success and the difficulty in transitioning from grating acuity to recognition acuity in young children. Even though children with NF1 are known to have a much higher rate of developmental delay and ADHD, we were surprised that the success rate of completing either test was not associated with the diagnosis of NF1 when accounting for subject age.

The success rate of the ATS computer-based HOTV testing has previously been evaluated, but primarily as a screening tool for vision loss in population-based studies of otherwise well children.[5,7,26,27] In these population-based studies,[7,26,27] approximately 37 to 47% of children younger than 3 years of age could complete the HOTV testing, compared to none of the subjects in our study. In the same studies, the success rate for children who were 3 and 4 years old markedly improved to nearly 85%,[7,26,27] whereas only half of our subjects could complete HOTV testing. Even when half of the study subjects have eye conditions resulting in decreased VA,[5] the success of computer-based HOTV testing is similar to larger studies comprised of primarily well children.[7,26,27] Our subjects typically have two to four eye exams per year for their clinical care, so their success rate may potentially have been lower if they were completing the testing for the first time. Unfortunately, we did not record the number of previously completed ophthalmologic exams or the testing method used. For children with NF1, we suspect our low success rate (i.e., 30.1%) is due to the known cognitive and behavioral comorbidities of this condition.[22,28] The treatment of OPGs, especially radiation, is known to cause cognitive side effects in young children and would likely be associated with VA testing success.

For children who could complete both TAC and HOTV testing, there was a strong correlation and coefficient of determination between logMAR scores. More specifically, the strength of this relationship is supported by the high adjusted coefficient of determination, suggesting that other factors

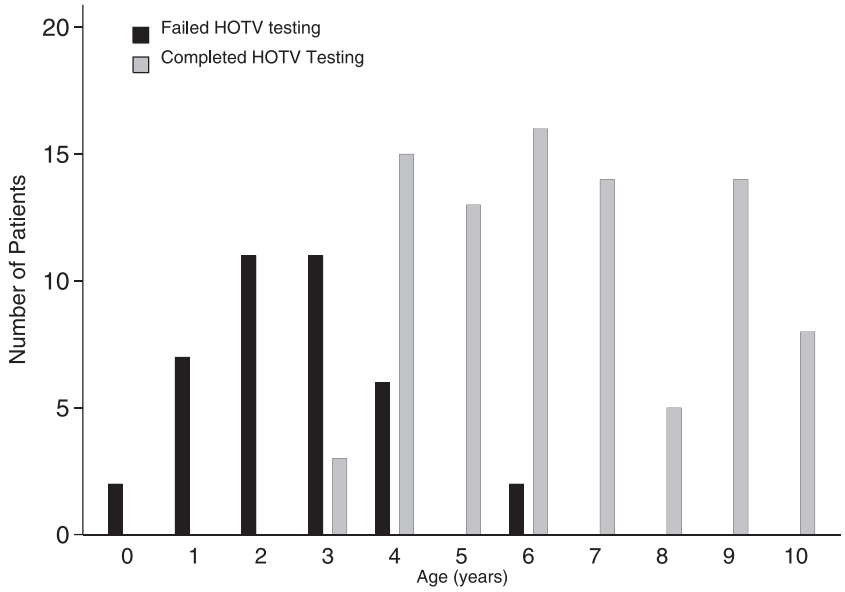

Figure 1. Relationship of age to success of completing HOTV.

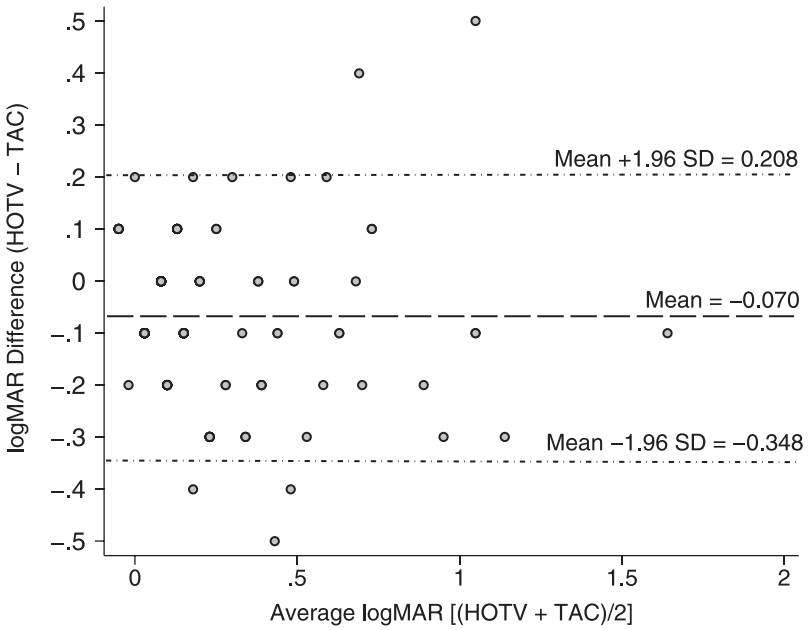

Figure 2. Bland-Altman plot in subjects able to complete both HOTV and TAC ($N = 161$ eyes; plot contains multiple overlapping points).

included in the regression model did not significantly alter this result. Our correlation coefficients were nearly identical to those from a study of premature infants who completed both TAC and HOTV testing at 4 years of age, although their analysis included mostly children with normal VA.[29] Birch and Spencer find an even higher correlation between TAC and Snellen acuity in a small group of children with a history of cicatricial retinopathy of prematurity (ROP).[30] Despite the differences in testing protocols as well as patient populations, our study and others[29,30] suggest that grating acuity and recognition acuity are closely related. On the other hand, data from a large multicenter study of children followed for ROP suggest that the ability of TAC to predict future recognition acuity is much more limited, primarily due to the test–retest variability.[11,31] When categorizing grating and recognition acuity into a binary category (i.e., normal versus abnormal), most investigators agree that an abnormal TAC is predictive of future abnormal recognition acuity.[11,17] Contrary to Kushner,[17] Dobson and colleagues contend that a normal TAC has a high likelihood of normal Snellen recognition acuity in the future since over 85% of their subjects with normal TAC eventually demonstrated normal Snellen recognition acuity.[11]

Our study had a number of limitations that should be considered when interpreting the results. Having four different examiners from two separate study sites perform the VA testing could certainly have affected the VA results. For example, some examiners may have had a higher success rate of completing the VA testing. Although a single designated examiner may have reduced testing variability, the correlation between TAC and HOTV remained strong and the success of testing did not differ between centers. Second, we did not routinely document the incidence of developmental delay and ADHD since it has been well established that at least half of all children with NF1 have some degree of intellectual and cognitive impairment.[22,23] Most clinicians defer making a formal diagnosis of ADHD until the child has been enrolled in elementary school. Since approximately half of our subjects had not yet entered elementary school, limiting this diagnosis to half of our study population would have been problematic. While the incidence of developmental delay and ADHD is likely associated with both the success and comparison between VA testing methods, our prospective study design and large sample size should have resulted in a representative population of children with NF1 and/or OPGs. Since both of our hospitals have dedicated NF1 and OPG centers, it is conceivable that some amount of referral bias resulted in our subjects having a higher incidence of these comorbid conditions.

The longitudinal assessment of VA in young children with OPGs is complicated by a number of factors. First, children with OPGs may enter a clinical trial at various ages and developmental stages, resulting in subjects enrolled with different success rates in performing TAC or recognition acuity. The strong relationship between TAC and HOTV logMAR in our current study provides further support to our previous recommendation that all pediatric OPG clinical trials test patients using TAC and, when the subject is developmentally able, also include HOTV.[24] Having subjects transition from grating acuity testing to recognition acuity testing, or even transition within recognition acuity methods (i.e., HOTV to Snellen), is problematic since their results are not equivalent, thereby complicating the analysis and interpretation of both short-term and long-term results.[8,11,16,17] Second, the mechanism and natural history of vision loss in children with OPGs is dynamic compared to vision loss from ROP, which is static after the perinatal period. Vision loss from OPGs can occur at any age, can be separated by many months or years, and can vary in severity. Therefore, categorizing VA loss as normal or abnormal, as in ROP, is not acceptable because a binary rather than continuous VA outcome would eliminate any meaningful longitudinal assessment of VA change. Some investigators have calculated the interocular difference in TAC to detect and measure the magnitude of vision loss.[8] Unfortunately, a majority of OPGs are located in the optic chiasm and tracts, putting both eyes at risk for vision loss. Last, an overwhelming majority of children who are being monitored for their OPG are younger than 8 years of age and are still experiencing normal visual maturation. It is unclear how the study design and statistical analysis plan should account for normal visual development.

In conclusion, the aforementioned factors highlight the difficulties in the longitudinal assessment of VA in children with OPGs and the need for a different approach to assessment than is used with other pediatric ophthalmologic diseases. For these reasons, and based on the data presented in the current study, it is still important to limit the VA testing methods to TAC and, when the children are old enough, to also test using HOTV, until a larger multicenter longitudinal clinical trial of children with OPGs can confirm that the VA measures are comparable and that the transition between methods will not significantly alter the results.

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