Published in final edited form as:

J Child Neurol. ; : 8830738251361698. doi:10.1177/08830738251361698.

Cortical Visual Impairment Across a Range of Neurodevelopmental Disorders (NDD): Clinical Characterization, Diagnostic Tool Evaluation, and Association with Developmental Outcomes

Megan Abbott, MD[a,c], **Katie Angione, MS, CGC**[a,c], **Megan Stringfellow, BS**[b], **Kristina Malik, MD**[b,d], **Margarita Saenz, MD**[b,e], **Emily McCourt, MD**[b,f], **Lori Silveira, PhD**[c], **Andrea Miele, PhD**[b,c], **Tim. A. Benke, MD, PhD**[b,c], **Scott Demarest, MD, MSCS**[a,c]

[a]Precision Medicine Institute, Children's Hospital Colorado Anschutz Medical Campus, Aurora 13123 East 16th Avenue Aurora, CO 80045

[b]Children's Hospital Colorado Anschutz Medical Campus, Aurora 13123 East 16th Avenue Aurora, CO 80045

[c]University of Colorado | Anschutz Medical Campus School of Medicine, Department of Pediatrics, Section of Neurology Anschutz Medical Campus, Aurora 13001 E 17th Pl Aurora, CO 80045

[d]University of Colorado | Anschutz Medical Campus School of Medicine, Department of Pediatrics, Section of General Academic Pediatrics Anschutz Medical Campus, Aurora 13001 E 17th Pl Aurora, CO 80045

[e]University of Colorado | Anschutz Medical Campus School of Medicine, Department of Pediatrics, Section of Genetics Anschutz Medical Campus, Aurora 13001 E 17th Pl Aurora, CO 80045

[f]University of Colorado | Anschutz Medical Campus School of Medicine, Department of Ophthalmology, section of Pediatric Ophthalmology Anschutz Medical Campus, Aurora 13001 E 17th Pl Aurora, CO 80045

Abstract

Cortical visual impairment (CVI) is particularly relevant in children with neurodevelopmental disorders (NDDs) yet remains underdiagnosed. This study assessed the prevalence and severity of CVI in four neurogenetic conditions: STXBP1, SLC6A1, Ring 14, and 8p-related disorders. We also evaluated the CCSA-Clinician vision subdomain (CCSA-vision) as a diagnostic tool and examined the association between CVI and developmental outcomes. A retrospective chart review of 85 patients found CVI in 44%, most commonly in 8p (54%) and STXBP1 (50%); no cases were seen in SLC6A1. The CCSA-vision subdomain effectively distinguished CVI cases

Corresponding Author: Megan Abbott, MD, Department of Child Neurology, Children's Hospital Colorado, Anschutz Medical Campus, Aurora, 13123 East 16th Avenue, Aurora, CO 80045, (Present/Primary): megan.abbott@childrenscolorado.org, Fax: 720-777-7285.

Ethics approval and consent to participate

This study was approved by Colorado Multiple Institutional Review Board (COMIRB 16-0152).

(mean score 25.9 vs. 2.6, $p < 0.0001$). A cutoff score ≥11 showed high specificity (95.9%) and positive predictive value (94.3%). CVI was significantly associated with greater developmental impairment, with higher overall CCSA scores and lower VABS-3 scores. Early identification of CVI is critical for ensuring access to appropriate therapies and therefore should be more systematically evaluated for in neurogenetic conditions.

Keywords

cortical visual impairment; neurodevelopmental disorders; Developmental and Epileptic Encephalopathies

1. Introduction

Cortical visual impairment (CVI)—also known as cerebral visual impairment or brain-based visual impairment (BBVI)—is the leading cause of pediatric visual dysfunction in the United States. It affects approximately 3% of children in the general population and at least 10% of those with developmental delays.[1–3] CVI was recently defined as visual impairment resulting from brain abnormalities, despite intact ocular structures and function, or visual deficits that are disproportionate to coexisting ocular conditions.[3,4] The diagnosis of cortical visual impairment (CVI) is primarily clinical, based on historical features such as inconsistent visual attention when reaching for objects, difficulty with ambulation over uneven surfaces or stairs, and visual behaviors like fixation on bright lights or specific colors, particularly red.[5] A diagnosis of exclusion approach is often used, and CVI is considered when visual dysfunction (as defined by exams, objective measures i.e. optokinetic nystagmus (OKN), structured history taking) cannot be fully explained by ocular findings.[6] Barriers to diagnosis include the lack of standardized diagnostic guidelines, limited numbers of trained professionals, and state-level restrictions on the type of specialist permitted to make the diagnosis.[7] As a result, many children with neurodevelopmental disorders (NDDs) with CVI go undiagnosed.[8]

The presence of CVI has been shown to negatively impact children's learning, especially reading function, as well as increase the incidence of behavioral challenges.[9] The relationship between CVI and developmental outcome was recently investigated in another NDD, *CDKL5* Deficiency Disorder (CDD).[10] Using a novel CVI and developmental score, CVI severity was shown to have a strong correlation with developmental attainment, even when controlling for other factors such as age and seizure burden.[11] Thus, a diagnosis of CVI has the potential for broad implications for both neurodevelopmental and educational trajectories. Understanding how CVI correlates with—and potentially impacts—development in individuals with NDDs is essential for guiding appropriate interventions and therapies. Clinical diagnosis of CVI is also necessary in order to obtain federally mandated services through school districts in the United States, such as a teacher of the visually impaired.[12] CVI must therefore be identified early, especially in children with neurogenetic diagnoses, to optimize their chance at visual rehabilitation and success.[13,14]

Individuals with NDDs were evaluated in the Neurogenetic Multidisciplinary Clinic at Children's Hospital Colorado. Among the conditions seen—*STXBP1, SLC6A1*, Ring 14,

and 8p-related disorders—cortical visual impairment (CVI) has been infrequently reported in the literature.[8] In *STXBP1*, CVI has been considered a rare phenotypic element.[15] In a large study of 8p-related disorders, CVI was reported in about 12% of patients.[16] CVI has not been reported in *SLC6A1* or Ring 14 cohorts. Because the presence of CVI has potential implications for learning and development, this study sought to explore the prevalence and severity of CVI in these populations. A clinical severity scoring system was then piloted for the diagnosis of CVI, assessing its sensitivity/specificity and predictive value. Finally, the relationship between CVI and developmental outcome was investigated to determine whether CVI severity correlates with lower developmental attainment broadly across these NDDs.

2. Materials and Methods

A retrospective chart review was completed on all patients who were seen and consented in the Neurogenetic Multidisciplinary Clinic at Children's Hospital Colorado from 2020 through 2024 (COMIRB protocol 16-0152). Clinical data was collected including demographics, detailed genotype, Vineland Adaptive Behavioral Scales-Third Edition (VABS-3), clinician's diagnosis of CVI (yes/no), reports from prior ophthalmological exam, and the patient's *CDKL5*-Clinical Severity Assessment-Clinician (CCSA-Clinician) score. The CCSA-Clinician is a validated clinician reported outcome measure with video-based training materials for a specific NDD, *CDKL5*-deficiency disorder.[17,18] CCSA-Clinician was administered prospectively to all patients by a trained assessor as part of clinical visits. The CCSA-Clinician includes the following domains: Motor, Communication, and Vision. The CCSA-vision domain includes the following items: fixing and following, optokinetic nystagmus reflex, eye alignment, and eye movements (nystagmus). Scores for each item were calculated on a scale of 0-100, with 100 representing the most severe impairment (Figure 1). The VABS-3[19] is an individually administered measure of adaptive behavior that has been widely used in the assessment of individuals with intellectual, developmental, and other disabilities. Caregivers completed the comprehensive, parent/caregiver form.

Data was entered into a secure RedCap[20,21] database. CVI prevalence was determined based on documentation in the neurologist's clinical note. All neurologists in this clinic are trained in CVI assessment which is informed by both exam and history. In our practice, a CVI diagnosis is only assigned if an eye exam by an ophthalmologist or optometrist is available. Patients without a documented eye exam were not considered to have a confirmed diagnosis of CVI. Descriptive statistical analysis was then performed on the group as a whole and each sub-group (*STXBP1*, *SLC6A1*, 8p, and Ring 14) including mean, median, and range. For continuous variables, comparisons between groups were calculated using t-tests. An ROC curve was generated (R version 4.5.0), evaluating the performance of the CCSA-vision domain in diagnosing CVI. A cut point score of 11 was calculated using the Index of Union method.[22] A score of 11 maximized sensitivity and specificity values with as little difference between the two values as possible (i.e. closest to upper left corner of ROC curve). Sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated utilizing a score of 11 or greater on the CCSA-vision domain. As an estimate of overall disease severity, the average CCSA scores of the other two domains (communication and motor) were calculated. VABS composite mean and

subdomain means were calculated for the CVI and no CVI groups. Comparisons of means were calculated using t-tests with significance set at a p-value of < 0.05.

3. Results:

3.1 Rates of Cortical Visual Impairment – Clinical Diagnosis

A total of 91 patients were seen and consented in the Neurogenetic Multidisciplinary Clinic from 2020 through 2024. Five patients were excluded from this analysis for having underlying ocular abnormalities (i.e. coloboma, cataracts); one patient was excluded for having an incomplete data set (Figure 2). Of these 85 patients, 37 (44%) were documented to have a diagnosis of CVI. The average age of those with CVI was 11.33 (SD +/−8.57) years compared to those without which was 9.37(SD+/−7.62) years (p-value=0.268). CVI rates for each population were as follows: 8p 14/26 patients (54%), *STXBP1* 21/42 patients (50%), *SLC6A1* 0/10 patients (0%), Ring 14 2/7 patients (29%) (Table 1).

3.2 Clinical Severity Assessment Score and CVI

Mean CCSA-visual subdomain score was higher in the patients with a confirmed diagnosis of CVI (25.9 +/− 15.4 SD), regardless of genetic diagnosis, when compared to the group without a diagnosis of CVI (2.6 +/− 4.6 SD). Mean visual subdomain scores in those with CVI are reported in Table 1 and visualized in Figure 3. 78% of patients without CVI across all disorders had a visual subdomain score of 0.

3.3 Performance of CCSA-vision in predicting a diagnosis of CVI

Utilizing the Index of Union method on the ROC Curve depicted (Figure 4), a score of 11 or greater on the CCSA-vision was used to indicate a likely diagnosis of CVI. Using this set point, sensitivity and specificity as well as PPV and NPV was calculated (Table 2), demonstrating high specificity for CVI and reasonable sensitivity as well. The CCSA-vision had a low false negative rate (7%) as well as false positive rate (1%).

3.4 Developmental outcome correlations

The overall CCSA score (communication and motor score average) was higher (indicating higher overall severity) in the group with CVI (45.0 (+/− 14.4 SD) vs 18.7(+/− 13.3 SD) (p value=0.0001) (Figure 5). On the VABS-3, means for the overall composite (Adaptive Behavioral Composite, ABC) and each sub-domain (standard scores (SS) where the mean is set at 100 with a standard deviation of 15.) were statistically lower in the CVI group (Table 3). Specifically, CVI ABC=39; No CVI ABC=60 (p-value <0.0001), Communication (SS=26 vs 55, p-value <0.0001), Daily Living Skills (SS=38 vs 60, p-value 0.0001), Socialization (SS=43 vs 64, p-value 0.0001), and Motor skills (SS=42 vs 71, p-value <0.0001).

Discussion

This is the first study to assess the prevalence of CVI across a range of neurogenetic conditions, evaluate a standardized clinical assessment for the identification and diagnosis

of CVI, and investigate the relationship of CVI and developmental attainment in these conditions.

Although previously thought to be a rare phenomenon in neurogenetic conditions,[23] these findings suggest that CVI is a common feature in many neurogenetic conditions and should be evaluated more systematically across all neurogenetic disorders. This is meaningful as CVI has been shown to lead to greater developmental challenges in neonatal cohorts,[24] as well as impaired quality of life[25] and motor development.[26] Early diagnosis of CVI is crucial to improving access to necessary therapies in time to make progress during critical developmental windows.[27,28] However, as CVI was not found in the *SLC6A1* cohort, it is important to note that CVI is not a characteristic of every neurogenetic condition. Careful evaluation of each individual is needed to determine the presence or absence of CVI.

Historically, identification of CVI has been limited in part due to a lack of standardized clinical tools to support the diagnosis of CVI in individuals with neurogenetic conditions. This study establishes the CCSA-vision domain as a helpful tool to support a clinical diagnosis of CVI by neurologist in conjunction with a normal ophthalmologic exam. While previously studied in CDD,[17,18] the CCSA had not previously been investigated in other conditions. In addition to a structured history, the components that make up the CCSA-vision are common components used to diagnose CVI and can be performed as part of a standard neurologic exam in clinic.[6,11,29,30] Scores on the CCSA-vision were significantly higher in the total group with CVI as well as all sub-groups analyzed with CVI. A cut off point of 11 or higher on the CCSA-vision was calculated to indicate a diagnosis of CVI as stated above, showing high specificity and PPV for CVI. Given these metrics, the CCSA-vision is a reliable confirmatory test in conjunction with clinical history, eye exam, and the overall assessment of the patient for a diagnosis of CVI. This diagnosis is important for referral to appropriate federally mandated educational services.

The CCSA-clinician motor and communication domain scores were higher in the CVI group suggesting higher severity of neurologic symptoms overall. Similarly, the VABS-3 demonstrated worse adaptive behavior not only for the overall composite score, but also in all domain scores. In summary, although the data does not support a causal relationship between CVI and increased overall developmental severity, it does demonstrate a significant association, indicating that individuals with CVI exhibit greater overall functional impairment.

This study is somewhat limited by the relatively small sample size, especially in the *SLC6A1* and Ring 14 subgroups. Utilizing the CCSA Communication/Motor domains as an overall marker of severity has not been validated outside of CDKL5 Deficiency Disorder and should be interpreted with caution. However, use of this measure is corroborated by similar associations in adaptive function using the VABS-3. While the CCSA-vision was used in four somewhat different neurogenetic conditions, this is only a small subset of greater than 6,000 neurogenetic conditions with a broad spectrum of presentations.[31] Larger samples and diversity of conditions would be required to validate this scale as a tool for diagnosing CVI across all neurogenetic conditions, potentially starting with a smaller subset of neurogenetic conditions such as developmental epileptic encephalopathies (DEEs).

Conclusions:

This study demonstrates a high prevalence of CVI across several neurogenetic conditions. These findings highlight the importance of screening for CVI in neurogenetic disorders and suggest the CCSA vision assessment may be a useful diagnostic tool clinically. CVI correlated with worse overall developmental scores, including those measured by the CCSA-communication and motor scores as well as a well validated and utilized caregiver reported measure. Future research involving larger cohorts is needed to further elucidate the factors driving this association and to clarify the role of CVI in shaping neurodevelopmental outcomes. Clinically, earlier recognition and systematic assessment of CVI may inform targeted interventions and improve support for children with neurodevelopmental disorders.

Acknowledgements:

The authors appreciate the continued support of our patients and their families

Funding:

This work was supported by funding from Project 8P, SLC6A1 Connect, Ring 14 USA, and STXBP1 Foundation, NIH/NINDS U01NS114312 (SD, TAB), Neuroscience Administrative Research Team (LS), and the Children's Hospital Colorado Foundation Ponzio Family Chair in Neurology Research (TAB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

Dr. Benke has received research funding from GRIN2B Foundation, the International Foundation for CDKL5 Research, Loulou Foundation, the National Institutes of Health, and Simons Foundation; consultancy for Alcyone, AveXis, GRIN Therapeutics, GW Pharmaceuticals, the International Rett Syndrome Foundation, Marinus Pharmaceuticals, Neurogene, Ovid Therapeutics, and Takeda Pharmaceutical Company Limited; clinical trials with Acadia Pharmaceuticals Inc., GW Pharmaceuticals, Ionis, Marinus Pharmaceuticals, Neurogene, Ovid Therapeutics, and Rett Syndrome Research Trust; all remuneration has been made to his department.

Scott Demarest: has consulted for Biomarin, Neurogene, Marinus, Tysha, Ultragenyx, UCB, Capsida, Encoded, Longboard, Mahzi therapeutics, Biogen, and Ovid Therapeutics; all remuneration has been made to his department. He has funding from the NIH, Project 8P, and Batten Disease Support and Research Association, and Mila's Miracle Foundation.

Andrea Miele has consulted for Biogen, Inc, Catalyst Pharma, Encoded Therapeutics, and Capsida Therapeutics; all remuneration has been made to his department. She has funding from Project 8P and the STXBP1 Foundation.

Megan Abbott has consulted for Acadia Pharmaceuticals; all remuneration has been made to his department. She has funding from the Dravet Syndrome Foundation, FamilieSCN2A Foundation, Rocky Mountain Rett Association, and SYNGAP1 Research Fund.

References:

1. Kran BS, Lawrence L, Mayer DL, Heidary G. Cerebral/Cortical Visual Impairment: A Need to Reassess Current Definitions of Visual Impairment and Blindness. Semin Pediatr Neurol. Oct 2019;31:25–29. doi:10.1016/j.spen.2019.05.005 [PubMed: 31548020]
2. Williams C, Pease A, Warnes P, et al. Cerebral visual impairment-related vision problems in primary school children: a cross-sectional survey. Dev Med Child Neurol. Jun 2021;63(6):683–689. doi:10.1111/dmcn.14819 [PubMed: 33533021]
3. Sandfeld Nielsen L, Skov L, Jensen H. Visual dysfunctions and ocular disorders in children with developmental delay. I. prevalence, diagnoses and aetiology of visual impairment. Acta Ophthalmologica Scandinavica. 2007;85(2):149–156. doi:10.1111/j.1600-0420.2006.00867.x [PubMed: 17263780]

4. Chang MY, Merabet LB. Special Commentary: Cerebral/Cortical Visual Impairment Working Definition: A Report from the National Institutes of Health CVI Workshop. Ophthalmology. Dec 2024;131(12):1359–1365. doi:10.1016/j.ophtha.2024.09.017 [PubMed: 39572128]
5. Roman-Lantzy C. Cortical visual impairment: An approach to assessment and intervention. American Foundation for the Blind; 2007.
6. McConnell EL, Saunders KJ, Little JA. What assessments are currently used to investigate and diagnose cerebral visual impairment (CVI) in children? A systematic review. Ophthalmic Physiol Opt. Mar 2021;41(2):224–244. doi:10.1111/opo.12776 [PubMed: 33368471]
7. Choi SA, Kim YO. West syndrome with hyperkinesia and cortical visual impairment: A case report of GRIN1 encephalopathy. J Genet Med. 2021;18(1):55–59. doi:10.5734/JGM.2021.18.1.55
8. Bosch DGM, Boonstra FN, de Leeuw N, et al. Novel genetic causes for cerebral visual impairment. European Journal of Human Genetics. 2016/05/01 2016;24(5):660–665. doi:10.1038/ejhg.2015.186 [PubMed: 26350515]
9. Morelli F, Aprile G, Martolini C, et al. Visual Function and Neuropsychological Profile in Children with Cerebral Visual Impairment. Children (Basel). Jun 19 2022;9(6)doi:10.3390/children9060921
10. Benke TA, Demarest S, Angione K, et al. CDKL5 deficiency disorder. GeneReviews®[Internet]. 2024;
11. Brock D, Fidell A, Thomas J, Juarez-Colunga E, Benke TA, Demarest S. Cerebral Visual Impairment in CDKL5 Deficiency Disorder Correlates With Developmental Achievement. J Child Neurol. Oct 2021;36(11):974–980. doi:10.1177/08830738211019284 [PubMed: 34547934]
12. Lehman SS, Yin L, Chang MY. Diagnosis and care of children with Cerebral/Cortical visual impairment: clinical report. Pediatrics. 2024;154(6):e2024068465. [PubMed: 39558730]
13. Huo R, Burden SK, Hoyt CS, Good WV. Chronic cortical visual impairment in children: aetiology, prognosis, and associated neurological deficits. Br J Ophthalmol. Jun 1999;83(6):670–5. doi:10.1136/bjo.83.6.670 [PubMed: 10340973]
14. Boonstra FN, Bosch DG, Geldof CJ, Stellingwerf C, Porro G. The multidisciplinary guidelines for diagnosis and referral in cerebral visual impairment. Frontiers in Human Neuroscience. 2022;16:727565. [PubMed: 35845239]
15. Ospina LH. Cortical Visual Impairment. Pediatrics In Review. 2009;30(11):e81–e90. doi:10.1542/pir.30-11-e81 [PubMed: 19884281]
16. Okur V, Hamm L, Kavus H, et al. Clinical and genomic characterization of 8p cytogenomic disorders. Genet Med. Dec 2021;23(12):2342–2351. doi:10.1038/s41436-021-01270-2 [PubMed: 34282301]
17. Saldaris J, Weisenberg J, Pestana-Knight E, et al. Content Validation of Clinician-Reported Items for a Severity Measure for CDKL5 Deficiency Disorder. J Child Neurol. Oct 2021;36(11):998–1006. doi:10.1177/08830738211019576 [PubMed: 34378447]
18. Saldaris JM, Jacoby P, Downs J, et al. Psychometric evaluation of clinician- and caregiver-reported clinical severity assessments for individuals with CDKL5 deficiency disorder. Epilepsia. Oct 2024;65(10):3064–3075. doi:10.1111/epi.18094 [PubMed: 39190322]
19. Sparrow SS, Cicchetti DV, Saulnier CA, PsychCorp. Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) -- Complete Kit. PsychCorp; 2016.
20. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019/07/01/ 2019;95:103208. doi:10.1016/j.jbi.2019.103208 [PubMed: 31078660]
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009/04/01/ 2009;42(2):377–381. doi:10.1016/j.jbi.2008.08.010 [PubMed: 18929686]
22. Unal I. Defining an Optimal Cut-Point Value in ROC Analysis: An Alternative Approach. Comput Math Methods Med. 2017;2017:3762651. doi:10.1155/2017/3762651 [PubMed: 28642804]
23. Bosch DG, Boonstra FN, de Leeuw N, et al. Novel genetic causes for cerebral visual impairment. Eur J Hum Genet. May 2016;24(5):660–5. doi:10.1038/ejhg.2015.186 [PubMed: 26350515]

24. Sonksen PM, Dale N. Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes. Dev Med Child Neurol. Nov 2002;44(11):782–91. doi:10.1017/s0012162201002936 [PubMed: 12418621]

25. Chadha RK, Subramanian A. The effect of visual impairment on quality of life of children aged 3-16 years. Br J Ophthalmol. May 2011;95(5):642–5. doi:10.1136/bjo.2010.182386 [PubMed: 20852314]

26. Matsuba CA, Jan JE. Long-term outcome of children with cortical visual impairment. Dev Med Child Neurol. Jun 2006;48(6):508–12. doi:10.1017/s0012162206001071 [PubMed: 16700945]

27. Lehman SS, Yin L, Chang MY, et al. Diagnosis and Care of Children With Cerebral/Cortical Visual Impairment: Clinical Report. Pediatrics. 2024;154(6)doi:10.1542/peds.2024-068465

28. Reh RK, Dias BG, Nelson CA 3rd, et al. Critical period regulation across multiple timescales. Proc Natl Acad Sci U S A. Sep 22 2020;117(38):23242–23251. doi:10.1073/pnas.1820836117 [PubMed: 32503914]

29. Chang MY, Borchert MS. Advances in the evaluation and management of cortical/cerebral visual impairment in children. Surv Ophthalmol. Nov-Dec 2020;65(6):708–724. doi:10.1016/j.survophthal.2020.03.001 [PubMed: 32199940]

30. van Genderen M, Dekker M, Pilon F, Bals I. Diagnosing cerebral visual impairment in children with good visual acuity. Strabismus. Jun 2012;20(2):78–83. doi:10.3109/09273972.2012.680232 [PubMed: 22612357]

31. Mancuso M, Houlden H, Molnar MJ, et al. How to approach a neurogenetics diagnosis in different European countries: The European Academy of Neurology Neurogenetics Panel survey. Eur J Neurol. Jul 2022;29(7):1885–1891. doi:10.1111/ene.15320 [PubMed: 35271759]

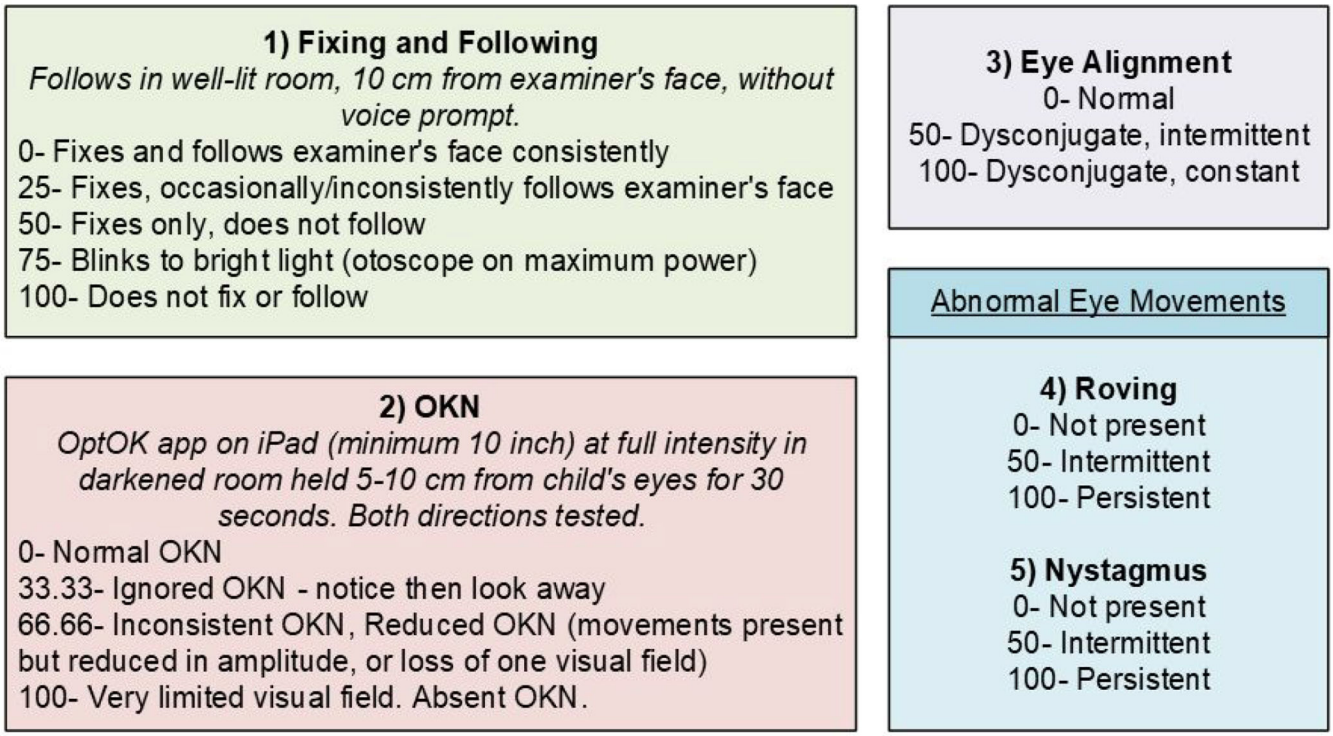

Fig. 1:
Items included in CCSA Visual Domain

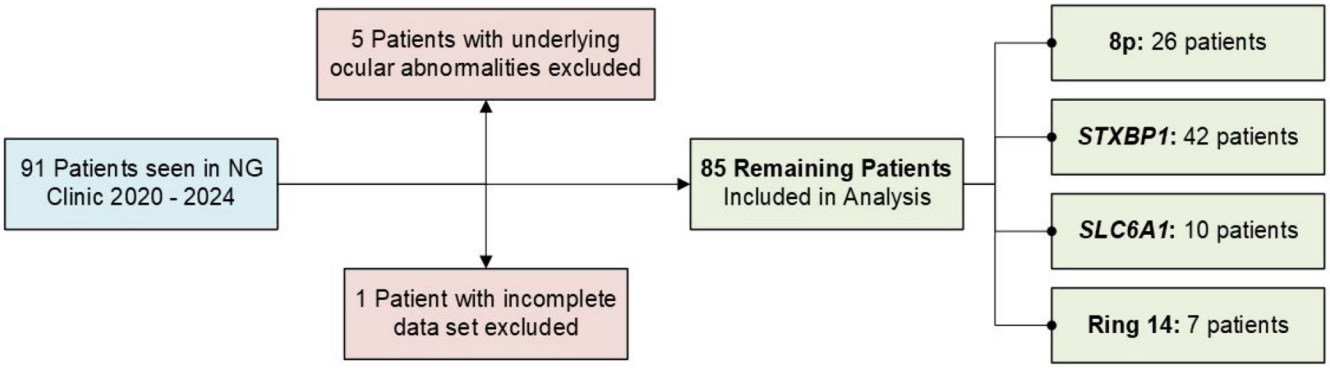

Fig. 2:
Study Population Flow Diagram

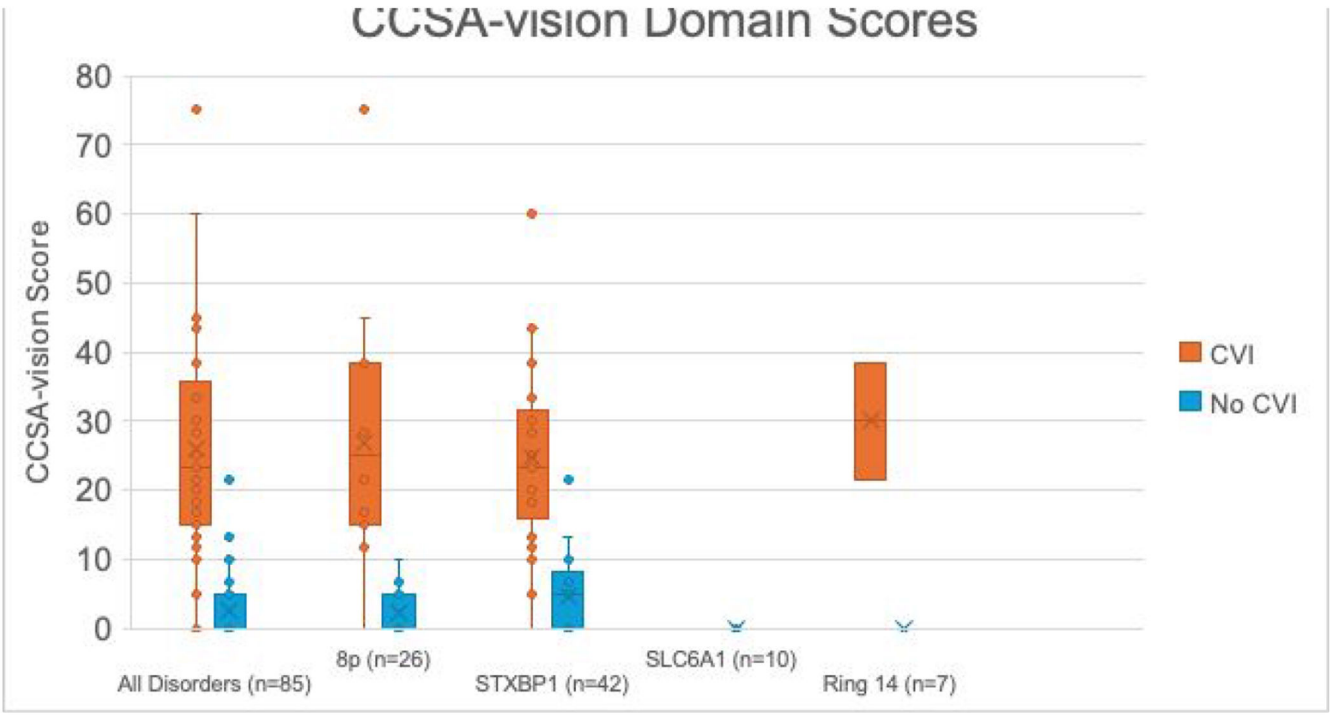

Fig. 3:
CCSA-vision scores across conditions

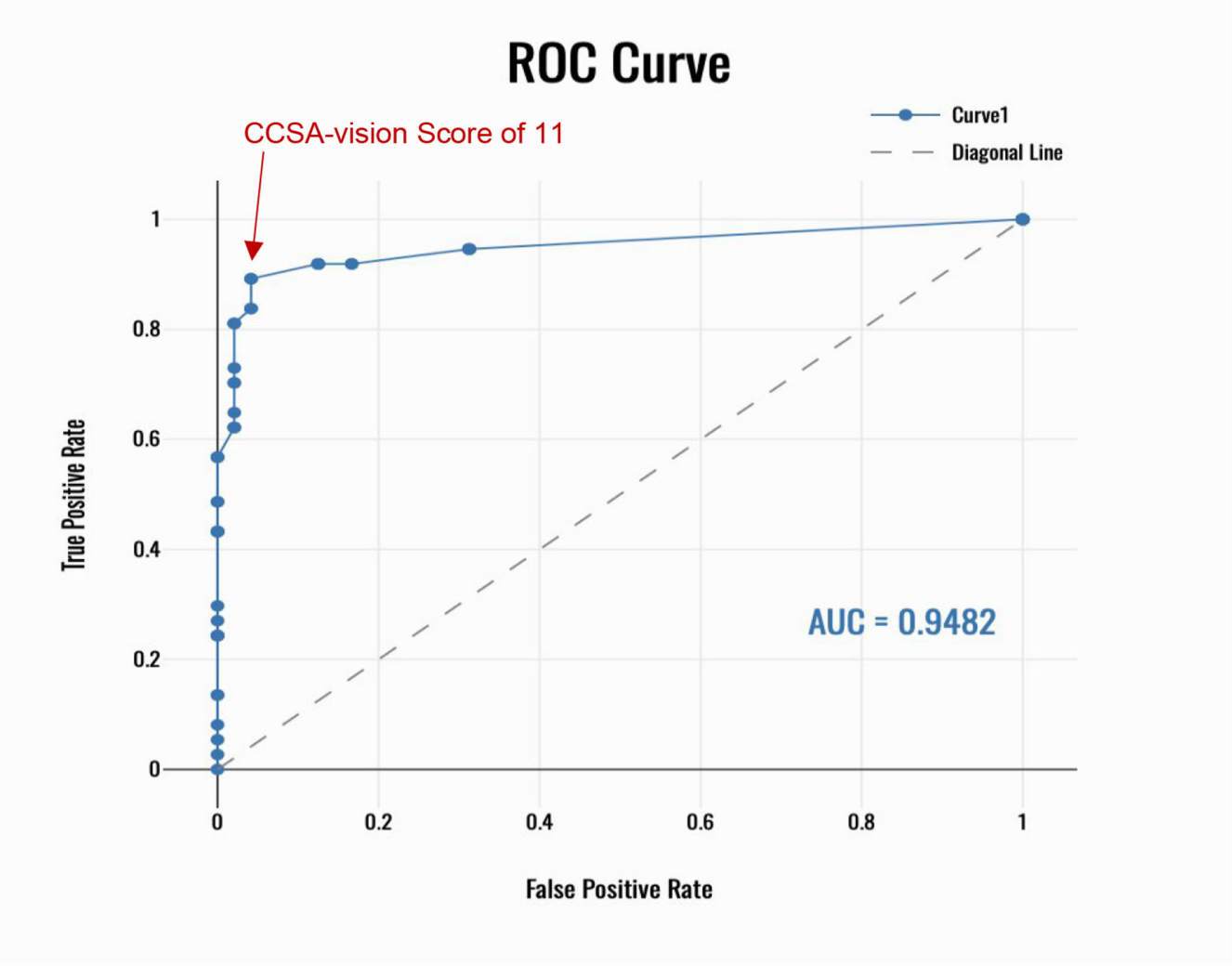

Fig. 4:
ROC Curve for CCSA-vision

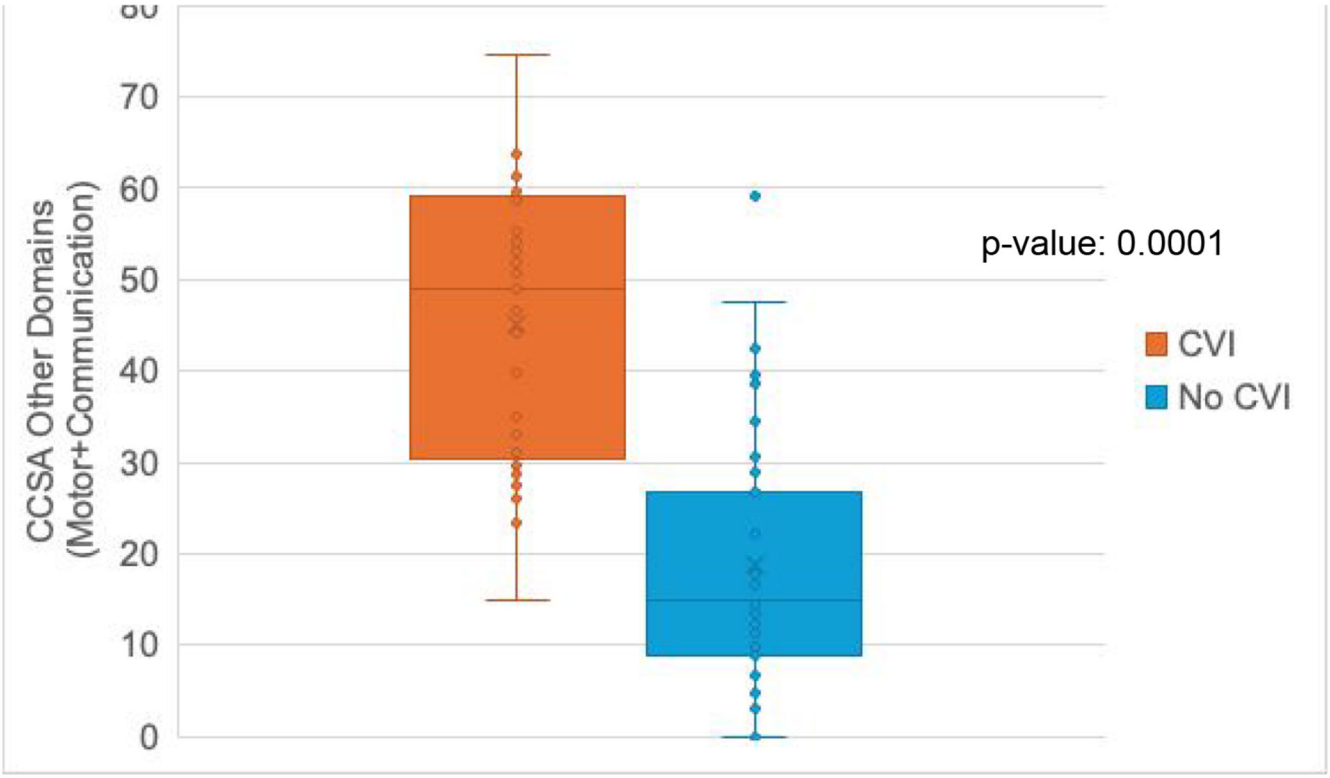

Fig. 5:
CVI and Overall Severity Score

Table 1:

CVI presence and score by disorder:

Group	CVI Present, n (%)	No CVI, n (%)	Vision Score** with CVI mean (+-SD)	Vision Score** without CVI mean (+-SD)	P value
Total	37 (44%)	48 (56%)	25.9 (+-15.4)	2.6 (+-4.6)	<0.0001*
8p	14 (54%)	12 (46%)	26.9 (+-18.4)	2.2 (+- 3.5)	0.0001*
STXBP1	21 (50%)	21 (50%)	24.8 (+-13.9)	4.6 (+-5.8)	0.0001*
SLC6A1	0 (0%)	10 (100%)	n/a	0	n/a
Ring 14	2 (29%)	5 (71%)	29.9 (+-11.8)	0	n/a

* = significant at p<0.05

** = CCSA-Visual Subdomain Score

Table 2:

Calculation of Sensitivity, Specificity and Predictive Values of CCSA-vision >= 11 for CVI

Statistic	Value	95% Confidence Interval
Sensitivity	89.9%	74.6-96.9%
Specificity	95.9%	86-99.5%
PPV	94.3%	80.9-98.5%
NPV	92.2%	82.3-96.7%

Table 3:

Vineland scores and CVI

Vineland Measure	CVI – mean (+-SD)	No CVI – mean (+-SD)	P-Value
ABC	39 (+-14.4)	60 (+-18.4)	<0.0001
Communication	26 (+-11.7)	55 (+-22.9)	<0.0001
Daily Living Skills	38 (+-20.3)	60 (+-13.8)	0.0001
Socialization	43 (+-18.7)	64 (+-21.0)	0.0001
Motor Skills	42 (+-14.2)	71 (+-12.5)	<0.0001