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Remote Assessment of Cognitive Function in Juvenile Neuronal Ceroid Lipofuscinosis (Batten disease) – a Pilot Study of Feasibility and Reliability

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Abstract

Remote technology provides an opportunity to extend the reach of clinical care and research for pediatric rare disease. This pilot study evaluated the feasibility and reliability of neuropsychological evaluation, using remote audiovisual technology, in the assessment of children with juvenile Batten disease. Three children with Batten disease and one healthy sibling completed a standardized cognitive assessment. Results indicated high agreement between an in-person and a remote evaluator, when comparing the subjects' cognitive test scores. This initial test of remote cognitive assessment suggests it is feasible and reliable in children with pediatric neurodegenerative disease, for whom disease burden may limit travel and access to expert care and/or clinical trials.

Keywords

Batten disease; CLN3; JNCL; telemedicine; neurodegenerative disease

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Author Contributions

Heather Adams and Shayne Ragbeer designed and executed the study, including data collection, analysis, and interpretation of data. All authors contributed to the preparation of the manuscript, including drafting and critical revision. All authors have provided final approval of the final version to be published.

Author's Note

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Declarations of Conflicting Interests

HR Adams and JW Mink are members of the Medical Advisory Board for the Batten Disease Support & Research Association; neither receives any financial compensation from the Batten Disease Support and Research Association for this role.

Ethical approval

This study was approved by the University of Rochester Research Subjects Review Board (RSRB00052942).

Introduction

Juvenile Neuronal Ceroid Lipofuscinosis (*CLN3*), also known as juvenile Batten disease, is an inherited, autosomal recessive, pediatric onset neurodegenerative disease caused by mutations in the *CLN3* gene.¹ Juvenile Batten disease is one in a group of neuronal ceroid lipofuscinosis diseases with genetically distinct etiologies and varying age at onset. For all genetic forms of childhood-onset Batten disease, the primary clinical symptoms are vision loss, loss of motor function, seizures, and a childhood-onset dementia characterized by cognitive regression and mood and behavioral problems.² Juvenile Batten disease is also considered a rare disease, with an estimated worldwide incidence ranging from 0.2 to 7.0 per 100,000.³

Because of its rarity, wide geographic dispersal, and the limited number of expert clinicians available, many individuals with Juvenile Batten disease must travel considerable distances to access specialist care or participate in clinical research. Currently, there are four designated Batten Disease Support and Research Association Centers of Excellence in the United States, including the University of Rochester Batten Center in Rochester, New York, that serve individuals with juvenile Batten disease and related conditions. In addition to providing patient care, the University of Rochester Batten Center conducts research visits using three different methods, each involving time, travel, and expense for families, investigators, or both.⁴ First, since 2002, University of Rochester Batten Center investigators have completed research visits with participants who attend the annual family support meeting hosted by the Batten Disease Support and Research Association; the meeting is held in a different part of the country each year. Second, since 2005, families have had the option to travel to the University of Rochester Batten Center in Rochester, NY. Unfortunately, because affected individuals become medically fragile with advancing disease, travel to either the University of Rochester Batten Center or annual Batten Disease Support and Research Association meetings becomes increasingly difficult over the course of the disease. Thus as a third method, University of Rochester Batten Center investigators have sometimes traveled to the homes of affected individuals for “research house calls”. The latter approach has also already been utilized in a recent randomized clinical trial of another rare and disabling pediatric disease – spinal muscular atrophy⁵. Beyond these two narrow examples of rare diseases (Batten disease; spinal muscular atrophy), there are an estimated 7,000 rare diseases that affect up to thirty million individuals worldwide. Among the impacts experienced by those with rare disease (and their family members and caretakers) are: diagnostic delays that on average may be as long as 7 years, lack of access to clinical and research experts, and a sense of isolation.⁶

Remote assessment can broadly refer to various assessment methods that do not require the direct physical presence of an examiner in the same location as the examinee. In at least one study, cognitive function was estimated remotely by a mail-in survey in which subjects self-rated their attention and memory skills. These self-ratings correlated significantly and positively with direct neuropsychological assessment.⁷ Evaluations of cognitive ability have also been performed by telephone, using either direct or “live” interaction with an examiner or with interactive voice response technology. Much of the research on telephone-based assessment has focused upon evaluation of older adults at risk for minor cognitive

impairment or Alzheimer's disease,⁸ but Plomin and colleagues have also evaluated (via telephone) cognitive abilities among large samples (~ 5,000) of school-age children.⁹⁻¹¹

More recently, internet access and computerized testing have further expanded options for remote cognitive assessment - as of 2012, approximately 79% of households had computers and 75% percent of American households had Internet access at their home.¹² Individuals may complete computerized testing that is either delivered via the internet or can be administered without an internet connection but is subsequently transferred via the internet or on a physical storage device for scoring and analysis. Additionally, examinees may complete assessment using a web-enabled camera that supports real-time video and audio connection with the examiner. In fact, the University of Rochester Batten Center has previously established reliability of a telemedicine assessment for the motor exam portion of the Unified Batten Disease Rating Scale, a disease-specific and quantifiable physical exam.¹³ However, cognitive assessment may present certain challenges. Children with Juvenile Batten disease experience vision loss, speech impairment resulting in poor articulation, and dementia, all of which could potentially limit remote cognitive assessment. Therefore, the aim of the present study was to pilot test the feasibility and reliability of a remote method for neuropsychological evaluation of individuals affected by juvenile Batten disease. To provide a context for the potential need for a reliable remote assessment method, we also evaluated the average distance travelled to the University of Rochester Batten Center by all individuals affected by juvenile Batten disease who have participated in our research studies since 2005. Our ultimate goal is to determine the feasibility and utility of remote assessment more broadly as a tool for evaluation of individuals affected by rare diseases, who require, but may have limited access to, expert clinical care and research opportunities.

Methods

Study Sample

The pilot telemedicine study was completed at the July 2013 annual meeting of the Batten Disease Support and Research Association, which took place at a hotel in Nashville, Tennessee. Adults and children were eligible to participate if they either had a confirmed genetic diagnosis of *CLN3*, or were a healthy (non-juvenile Batten disease affected) sibling of a person with genetically confirmed *CLN3*. The purpose of including healthy siblings was to determine if there were differences in the feasibility of the project, or the quality or quantity of data that could be obtained in individuals with versus without juvenile Batten disease.

Study Method

Each subject was assigned to one room, accompanied by a doctoral candidate graduate student in Psychology (SNR) with experience and training in the evaluation of children, including those with challenging behaviors (i.e., autism spectrum disorder). The graduate student also had prior research experience evaluating individuals with juvenile Batten disease, with training and supervision provided by the principal investigator (HRA) who observed evaluations directly and provided immediate corrective feedback as needed. In

another room on the same hallway, the investigator established a remote, telemedicine link with the subject and the graduate student. The principal investigator is a pediatric neuropsychologist with expertise in assessment of individuals with juvenile Batten disease. The investigator had over a decade's experience in the cognitive assessment of such children, with over 150 evaluations (in approximately 70 children with genetically confirmed Batten disease) at the time of the current study. The remote link was established using Vidyo. Vidyo is a proprietary software program that supports telemedicine through the use of a secure, Health Insurance Portability and Accountability Act-compliant internet-based audio and video link that operates through a standard laptop with either a built-in or external webcam.

With the investigator in one room, and the subject and graduate student in another, we performed remote neuropsychological assessment via one of two methods (Figure 1), selected at random (coin flip) for each of the subjects. Each method was designed to replicate what is likely to occur in real-world clinical or research settings for remote assessments of individuals with juvenile Batten disease. The following cognitive tests were performed: Wechsler Intelligence Scale for Children – Fourth edition¹⁴ Similarities, Vocabulary, Information, and Digit Span subtests; Wide Range Assessment of Memory and Learning – Second edition¹⁵ Story Memory subtest; Verbal Fluency test. We have previously established standard adaptations in administering these tests to children with juvenile Batten disease, to accommodate their vision loss.¹⁶ With each method, described in detail below, both the graduate student and the expert clinician independently recorded and scored all subject responses (i.e., the subject's answers to each question in the neuropsychological test battery).

Method 1 – Remote Expert Assessment with In-Person Technical Assistance

—The investigator remotely administered the neuropsychological testing, while the graduate student sat with the subject in the other room and provided technical assistance as needed. Technical assistance consisted of ensuring that the webcam was correctly positioned and the volume was adequate. In addition, the graduate student was available to redirect the subject's attention to the tasks (upon request from the investigator), and to provide verbatim clarification if the investigator indicated that she could not understand something that the subject had said, due to poor speech articulation. In the real-world analog of this method, an expert clinician would remotely evaluate the individual, while that person was locally based (i.e., at their home, school, or local clinical setting) and under observation by a parent, teacher, local psychologist, or other clinician.

Method 2 – In-Person Assessment with Remote Expert Guidance—The neuropsychological testing was administered directly by the graduate student, who was in the same room as the individual with juvenile Batten disease, while the investigator observed the evaluation through the remote connection. In the real-world analog of this method, a person might complete testing locally with a school- or clinical psychologist, but with an expert clinician available remotely and in real time, to provide guidance on the nuances involved in testing someone with juvenile Batten disease. Such guidance might take the form of prompts regarding behavioral management of individuals with juvenile Batten

disease, guidance on time allowances for verbal responses, or strategies to optimize comprehension of the affected individual's poorly articulated speech.

Evaluation of Travel Burden

Separately, we identified all individuals who completed at least one research or clinical visit at the University of Rochester Batten Center in Rochester, New York from 2005-2014. We calculated the total round-trip driving distance in miles from each participant's home (based on the home address zip code) to the University of Rochester Batten Center. This distance is considered an estimate of the total distance traveled for each family, some of whom traveled to Rochester via airplane. Because some families traveled to Rochester with more than one affected individual during the same University of Rochester Batten Center visit, we considered only the number of unique visits per family rather than the number of unique visits per affected person.

Data Analyses

Because of the small sample size, kappa coefficients were not generated. We evaluated the agreement between the two examiners (expert clinician and graduate student) for the score awarded for each item, on each neuropsychological test. This allowed calculation of the percent agreement between each examiner to determine inter-scorer reliability. Agreement for the verbal fluency task was calculated based on the total number of words generated by the child, across all five trials (F, A, S, animals, foods). In addition to percent agreement statistics, we calculated the average round-trip distance traveled (mean, standard deviation, range) by all families who have visited the University of Rochester Batten Center. All analyses were performed with Statistica ver. 12 (Statsoft, Tulsa, OK).¹⁷

Ethical Approval

All research activities were completed through a protocol approved by the University of Rochester's Research Subjects Review Board. Parents of all participating children provided written permission for their child's involvement in the study. Given the impact of juvenile Batten disease on decisional capacity, a waiver of assent or consent, respectively was granted for affected participants. Healthy unaffected siblings participated in an informed assent/consent process as appropriate for their age.

Results

Three male children with genetically confirmed juvenile Batten disease, and one non-affected male sibling of an affected child, participated in this study. The average age of the four children was 14.3 years (SD = 2.8; range = 10.6 – 16.6 years). Table 1 shows the percent agreement for each test, averaged across all items within each respective test. For all tests except one (Verbal Fluency), inter-scorer agreement was high, with agreement ranging from almost 78% to up to 100% between the examiners. Due to time limitations with some study visits, the Verbal Fluency task was only completed by two participants (one with juvenile Batten disease, and one healthy sibling), and had the lowest percent agreement value (60%), when considering between-scorer agreement. For each participant, the graduate student who was present in the room with the child recorded slightly more words than did

the investigator, who recorded the word count via the remote video link (child affected by juvenile Batten disease: N = 8 vs. 7 words; healthy child: N = 44 vs. 41 words). As shown in Table 1, between-scorer agreement improved for some cognitive tests when removing the healthy (non-Batten affected) child from analyses. All children also behaviorally tolerated the assessment, all subjects were fully compliant, and each completed all tasks that were presented.

Travel Burden

From 2005-2014, 58 children with genetically-confirmed juvenile Batten disease, from 51 families, visited Rochester, New York at least one time for an evaluation at the University of Rochester Batten Center. With multiple visits by some families, 102 evaluations of individuals affected by juvenile Batten disease were completed at the University of Rochester Batten Center during this time period. Because some families visited the University of Rochester Batten Center on multiple occasions with one or more affected children, there were a total of 78 unique trips (i.e., trips by a family) to Rochester. Of these 78 trips, the average round-trip distance for a single visit to the Center was 1,746.2 miles (Standard Deviation = 1324.2, Median = 1361.0, range = 362 – 5272). The present study, which reviewed historical data on travel distances to the University of Rochester Batten Center, was unable to determine direct per-subject costs for each of these in-person research or clinical visit. However, referencing national transportation statistics data for these same years of 2005-2014, the average round-trip airfare for two persons traveling to Rochester, NY (e.g., child with Batten disease, accompanied by one parent) was approximately \$650 (standard deviation = \$43; range = \$592 – \$770).¹⁸

Discussion

In this pilot study, we demonstrated initial feasibility and reliability of remote assessment for cognitive evaluation of children with juvenile Batten disease. Children tolerated the assessment and were able to complete all parts of the evaluation without difficulty. The technology also worked effectively, providing a seamless live video and audio connection between the two locations. Interestingly and unexpectedly, the percent agreement values were higher when excluding the healthy child. This was most noticeable on two tasks that required detailed transcription of extensive verbal responses. When *including* the healthy child, percent agreements were lower for the Verbal Fluency task and the Wechsler Vocabulary task. To score each of these tasks, the examiner must rapidly and accurately transcribe verbal responses that are more detailed and less predictable (i.e., with the potential for a broader set of responses) than the other tasks that were presented. Subsequent debriefing between the scorers identified a possible reason for the relatively large difference in percent agreements for these two tasks; the healthy, non-JNCL affected child spoke rapidly and was physically active during the evaluation, including moving out of the camera frame at times, which made it difficult for the remote examiner to hear all responses. In future clinical or research applications of remote cognitive evaluations, there may be additional strategies to enhance accuracy and completeness of the assessment. Suggestions include audio-recording and subsequent transcription of subject responses, and/or adding a microphone directly to the subject to ensure audio quality regardless of their

position relative to the remote technology equipment (e.g., laptop with webcam). Remote technology itself may aid in full data capture; for example, when subjects' unexpectedly cannot travel to a research site for a scheduled visit, or who could not complete all planned activities during a site-based visit.

Results of this preliminary study appear consistent with prior investigations of remote evaluation of cognition. Among adults, remote assessment has been established as reliable and valid for cognitive evaluation of minor cognitive impairment, memory disorders and dementia¹⁹⁻²¹. Remote cognitive assessment of adult-onset dementias by telephone or videoconferencing has been demonstrated to be as accurate as in-person evaluation and correlates well with standard cognitive assessments such as the Mini-Mental Status Exam.^{22,23} Telemedicine delivery of health care is also rated by patients and caregivers as satisfactory^{24,25}. In addition, remote assessment has been used to obtain estimates of cognitive function in intellectually disabled adults - Temple et al.²⁶ found on average only one Intelligence Quotient point difference between remote versus in-person evaluations, which is negligible. There is less known about remote cognitive assessment of children. Waite et al.^{27,28} explored the use of remote videoconferencing to evaluate expressive and receptive language, reading, spelling, and other literacy skills in school-age children. Though the investigators noted some technical challenges such as audio quality and audio lag-time that impacted some components of the evaluation, in general the results indicated very good agreement between in-person and remote evaluations, and high overall reliability.

Further research is needed in both healthy children and among those with various health conditions, to definitively establish reliability and validity of remote cognitive testing, and to delineate the most appropriate assessment tasks for remote evaluation. For example, children with substantial developmental delay or behavioral difficulties may require direct, in-person evaluation by a clinician with expertise in both the disease and in assessment, as well as behavioral management skills. Among children with sensory impairments, assessments should of course be selected appropriate to the child's functional capacity. Fortunately, there are many existing reliable, valid assessments that can accommodate visual, hearing, or motor impairments(CITN); for example, in our research with juvenile Batten disease we utilize gold-standard assessments such as the Wechsler scales, administering only the verbal components of the test for these visually-impaired children.²⁹ Finally, we note that the selection of assessment measures appropriately matched to a child's sensory or motor functional capabilities would arise even for in-person assessment. Assessments of very young children typically involve the use of "hands-on" test stimuli (e.g., puzzles pieces) that could not be presented by a remote examiner. And, at any age, assessment of certain cognitive domains, such as visuomotor integration, will require hands-on stimuli (e.g., blocks) that could not be presented through remote assessment. However, in these instances, a skilled local technician could administer such tasks with remote expert guidance. For this reason, in our study we evaluated the feasibility of two options: remote cognitive assessment, (Figure 1A), and local assessment with remote supervision (Figure 1B). Though a local psychologist may have technical proficiency and general expertise in conducting assessment, disease-specific proficiency may be lacking. Both options that we explored support the involvement of a psychologist with disease-specific proficiency, when a family is unable to travel to a clinical or research setting in order to access such expertise face-to-

face. These two options allow a psychologist with disease-specific proficiency to administer the assessment with technical support from a local psychologist with general training in assessment (1A) or to allow a local, general psychologist to conduct assessment with supervision by the psychologist with disease expertise. expert psychologist. As with certification for proficiency with other research or clinical evaluation tasks, it would be useful to establish a period of training and supervision by an expert, followed by periodic audits to ensure ongoing consistency and reliability of assessments.

Beyond cognitive assessment, remote technology can be a useful tool to complete other elements of clinical research,³⁰ including evaluation of adaptive and behavioral function and delivery of behavioral interventions,³¹⁻³³ obtaining or reviewing safety data, or facilitating the enrollment and consent process.³⁴ In our own investigations, we have used remote telephone assessment to evaluate adaptive function in juvenile Batten disease.³⁵ In clinical trials of psychosocial interventions, remote technology is also now being utilized to deliver behavior therapy. Finally, using one or a small number of centralized, expert raters to conduct assessments remotely for multiple clinical research sites, it may be possible to minimize intra-examiner bias and inter-examiner variability, ultimately reducing error variance and improving data quality.^{36,37}

Remote assessment also has the potential to reduce study cost. As described above, the estimated average per-family (one parent and one child) costs for a single round-trip flight to visit the University of Rochester Batten Center was approximately \$650. By contrast, the current financial cost of our conferencing technology is \$100 monthly for unlimited use, or approximately 15% of one in-person clinical research visit by one subject (and accompanying parent) to our Center. Other potential and unaccounted-for cost considerations include the expense of using space at a local clinical or research site (for remote study visits) in comparison to using dedicated clinical research space at a centralized disease-expert study site.

Above and beyond the economic cost of remote versus direct visits are psychosocial and physical burdens imposed upon patients and their families when travel is required. For example, in all childhood onset forms of Batten disease, children become blind, lose independent ambulation, have seizures, and develop dementia.² The quality of the data obtained, and the motivation, effort, or ability of a child to participate adequately in cognitive assessment, may be compromised by the physical demands of traveling across country and across time-zones, to participate in a research visit far from the comfort of their own home. Though remote assessment may not be suitable for all persons or all types of evaluation, it may improve options for access among those with rare disease, who may have limited access to expert clinicians and researchers.

We acknowledge several limitations to this study, including the artificial nature of the remote assessment (tested in hotel rooms during a family support conference), and the small sample size. In this and other rare diseases, sample size limitations present a unique but unavoidable challenge, because of the overall low number of affected individuals in the disease population, and the smaller number still of those present at the location where this study was conducted. In fact, it is for these reasons that remote assessment has particular

appeal – because of its potential to extend the geographic reach of clinical care and clinical research to those with orphan conditions. In addition, we have not yet demonstrated reliability and validity of the remote assessment, though we also recognize this is challenging with rare diseases where sample size, and sampling opportunities, are limited. We are encouraged by prior studies that have established the psychometric properties of remote psychological evaluations, including cognitive assessment³⁸

In this pilot project, the graduate student had prior experience evaluating several children with JNCL, using the same neuropsychological protocol; this may have contributed to the high level of agreement between examiners. Local practitioners may lack this experience and may require additional training or supervision to ensure a similar comfort level in evaluating this challenging population. However, the initial agreement statistics with this small sample demonstrate that even among children with sensory, motor, and cognitive impairments, remote telemedicine may be a feasible strategy to obtain reliable cognitive test data.

We must underscore that the use of a reliable high-speed internet connection, and both software and hardware that can support high fidelity audio and video, with no discernible time lag, are essential. In a subsequent study location (the hotel site for the 2014 Batten Disease Support and Research Association conference) we attempted to complete additional remote assessment visits, but bandwidth limitations negatively impacted the quality of the video feed (screen freezing, lag times between video and audio, and loss of connection). Reliance on a public and heavily shared network, such as at a hotel where our research visits occurred, likely resulted in variable quality of the internet connection. These technological problems can be surmounted through a dedicated high-speed internet service and adequate software and hardware to support a high fidelity connection.

As summarized in a recent review, “virtual visits” that use videoconferencing technology have been reported in randomized, controlled trials of both pediatric and adult neurologic and non-neurologic conditions as feasible, comparable to in-person care for reliable assessment of physical or behavioral function, and rated by participants as an acceptable method for clinical or research visits.³⁹ In the present study, we have demonstrated that remote cognitive assessment is feasible in a rare, pediatric, neurodegenerative disease; this approach may have applicability to clinical trials and clinical care more broadly for other pediatric metabolic or neurodegenerative diseases. Our future telemedicine studies in Batten disease will evaluate virtual visits in the child’s home setting, and will also evaluate satisfaction and cost-effectiveness of such assessments. Ultimately, we view videoconferencing and other remote methods as additional tools to expand care and research for individuals affected with rare conditions, who might otherwise have very limited access to experts in their disease.

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Figure 1. Schematic for Remote and In-Person Cognitive Assessment of Subjects
Figure 1A. Method 1 – Remote Assessment with In-Person Technical Assistance
Figure 1B. Method 2 – In-Person Assessment with Remote Expert Guidance

Table 1

Percent Inter-scorer Agreement for Neuropsychological Test Items Administered Via Remote Assessment

Test Items	Percent Agreement (95% Confidence Interval) ALL SUBJECTS	Percent Agreement (95% Confidence Interval) ONLY SUBJECTS WITH juvenile Batten disease
WISC-IV Vocabulary	85.29 (68.94– 95.05)	100.00 (84.67 – 100.00)
WISC-IV Digit Span	100.00 (86.09 – 100.00)	100.00 (74.11 – 100.00)
WISC-IV Similarities	95.65 (78.05 – 99.89)	95.65 (78.05 – 99.89)
WISC-IV Information	100.00 (91.32 – 100.00)	100.00 (91.32 – 100.00)
Verbal Fluency	60.00 (14.66 – 94.73)	80.00 (28.36 - 99.49)
WRAML Immediate Recall	93.59 (85.67 – 97.89)	98.72 (93.06 -99.97)
WRAML Recognition	100.00 (92.78 – 100.00)	100.00 (92.78 – 100.00)

Footnote: WISC-IV: Wechsler Intelligence Scale for Children – Fourth Edition; WRAML-2: Wide Range Assessment of Memory and Learning – Second Edition.