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Methodology of clinical research in rare diseases: development of a research program in juvenile neuronal ceroid lipofuscinosis (JNCL) via creation of a patient registry and collaboration with patient advocates

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Abstract

Introduction—Juvenile neuronal ceroid lipofuscinosis (JNCL; Batten disease) is a rare, inherited, fatal lysosomal storage childhood disorder. True for many rare diseases, there are no treatments that impact the course of JNCL. The University of Rochester Batten Center's (URBC) mission is to find treatments to slow, halt, or prevent JNCL.

Objectives—Our initial objective was to develop clinical research infrastructure preparatory to clinical trials, establish a JNCL research cohort, construct a disease-specific clinical outcome measure, and validate a non-invasive diagnostic sampling method. The long-term objective is to design and implement JNCL clinical trials.

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Methods—The Unified Batten Disease Rating Scale (UBDRS) was developed. The Batten Disease Support and Research Association (BDSRA) referred participants; annual BDSRA meetings provided a mobile research setting for registry enrollment and UBDRS piloting. Neuropsychological examinations were performed, enabling external validation of the UBDRS. Buccal epithelial cell collection for genotyping was introduced. Telemedicine for remote UBDRS assessment was piloted.

Results—The registry enrolled 198 families representing 237 children with NCL. The UBDRS was piloted, validated and has been used to collect natural history data from 120 subjects. Funding and regulatory approval were obtained for a recently launched phase II clinical trial. Several additional lines of inquiry were reported.

Conclusion—The registry and BDSRA collaboration have enabled development of a clinical rating scale, natural history and neuropsychological studies, and genetic studies for disease confirmation. This work highlights an approach for preparatory natural history research and infrastructure development needed to facilitate efficient implementation of clinical trials in rare diseases.

Keywords

juvenile neuronal ceroid lipofuscinosis; rare disease; patient registry; clinical trials; patient advocacy; subject recruitment

Introduction

Juvenile neuronal ceroid lipofuscinosis (JNCL; *CLN3* disease; Batten disease) is a fatal, inherited, autosomal recessive lysosomal storage disorder of childhood with an estimated worldwide incidence of approximately 8 per 100,000 [1].Core symptoms of JNCL include vision loss, seizures, dementia, motor impairment, and behavioral and psychological problems. Symptoms begin between ages 5 and 8 years, with death during the second or third decade of life. There are no established treatments that slow, arrest, or reverse the disease course.

In addition to the juvenile form due to mutations in *CLN3* on chromosome 16p12.1, there are several additional forms of neuronal ceroid lipofuscinosis (NCL) due to mutations in other genes [2]. Together, the NCLs represent the most prevalent inherited neurodegenerative disease in childhood [3]. Nevertheless, NCLs are rare and each individual form is rarer still, presenting numerous challenges for advancing care and treatment [4]. There are similarities between the NCLs and other rare diseases where future success in therapeutic attempts to impact symptoms or disease progression relies on improved understanding of the clinical characteristics and nature of the disease process, as well as quantifiable endpoints to judge therapeutic efficacy [5, 6]. While randomized, double-blind clinical trials are considered the gold standard for assessing therapeutic benefit, there are challenges to the design and implementation of clinical trials in rare diseases, including statistical considerations for adequately powered clinical trials, due to the small numbers of individuals available for participation [7, 8].

Recruitment for studies in diseases in which the affected population is small and geographically dispersed can be aided by coordination and networking with patient advocacy organizations, particularly when a patient registry mechanism exists [9]. Voluntary patient contact registries, such as those developed as part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network Contact Registry, may help researchers identify and recruit patients who are eligible for participation in research studies [10]. A longstanding patient registry was developed by the Cystic Fibrosis

Foundation in the 1950's as a collection of personal data about patients with the disease and has evolved to a more sophisticated system that tracks treatment and health outcomes, enabling physicians, researchers, patients and their families to seek out treatment options and opportunities for clinical trial participation [11]. Patient registries can provide valuable data to help understand the etiology of rare diseases, the natural disease course and impact of therapy, and facilitate enrollment in clinical trials, all of which are important for the development of new diagnostics and therapeutics [12, 13].

The overarching aim of the University of Rochester Batten Center (URBC) is to find treatments to slow, halt or prevent the progression of JNCL. Via collaboration among the Batten advocacy community, researchers, patients and families, the URBC has made progress over the past 10 years in setting the stage for initiation of JNCL clinical trials via a patient contact registry, natural history database, and collaborative research initiatives.

Objectives

The URBC's initial objective was to develop a clinical research infrastructure preparatory to clinical trials, including establishment of a cohort of JNCL-affected children and their families willing to participate in clinical research. An important first step was to develop a system to 5 identify, register, and eventually recruit children and families into observational studies and clinical trials. An important first step was to develop a system to identify, register, and eventually recruit children and families into observational studies and clinical trials.

A second objective was to develop and validate a standardized disease-specific assessment tool for JNCL to characterize and quantify the various disease components and the natural history of their progression. Prospective, uniformly collected natural history data are essential for clinical trial development and have broad usefulness in clinical practice, as the data can be used as the basis for anticipatory guidance and to examine the impact of therapeutic interventions [14].

A third objective was to validate a non-invasive method for genetic testing to confirm the genotype of each participant in URBC studies. Confirmation of JNCL diagnosis due to *CLN3* mutations with molecular genetic testing is needed because a JNCL-like presentation has been noted in patients with deleterious mutations in the palmitoyl-protein thioesterase 1 (*CLN1*) or tripeptidyl peptidase I (*CLN2*) genes, which are usually associated with the infantile- or late infantile-onset forms of NCL, respectively [14–19]. Traditional blood sampling methods used in adults can be technically challenging in children and venipuncture can be unpleasant or even traumatic for a child; thus, non-invasive methods are desirable.

Lastly, as a long-term objective, the URBC sought to design and implement a clinical trial in Batten disease. The feasibility of designing a study involving geographically dispersed Batten-affected individuals, who suffer a range of physical, behavioral, and psychological disorders associated with the disease, was uncertain yet was an important objective towards the overall aim of the URBC .

Methods

The Batten Disease Support and Research Association (BDSRA; www.bdsra.org) is an advocacy group representing families throughout North America who are affected by Batten disease. The BDSRA annual conference for families has served as a mobile clinical research laboratory for the URBC since 2002, where a convenience sample of families has enrolled in the contact registry, the natural history and disease-specific rating scale study, and/or neuropsychological investigations.

The contact registry and all URBC research activities were conducted under protocols approved by the University of Rochester Research Subjects Review Board. Informed consent from parents/legal guardians of affected children was obtained for all research activities.

Registry Development

In order to establish a Batten cohort for a natural history study, the URBC developed a limited-content patient registry of NCL-affected children. The BDSRA provided financial support for registry development and assisted with recruitment; the registry maintenance has since been supported by NIH funding and by the University of Rochester Department of Neurology. Families of children with Batten disease willing to be contacted or release medical information for future research were included in the registry. Registrants agreed to be contacted by the URBC about future, unspecified clinical research including, but not limited to, clinical trials for JNCL.

To initiate participation in the registry, an introductory letter and survey form were used to record agreement of parent(s) or legally authorized representative(s) for data collection. Registry content includes: parent/guardian contact information and that of the affected child(ren)'s health care provider, year of birth and NCL sub-type, if known; no child names were provided. On an ongoing basis, parents/guardians of all new participants in the UBDRS study were also invited to enroll in the contact registry, as were families seen for clinical consultation at the URBC. Data were entered into a password-protected electronic database with access only to the principal investigator and project coordinator.

Unified Batten Disease Rating Scale (UBDRS)

The objective to develop and validate standardized tools to characterize JNCL was pursued via construction, pilot testing, refinement and validation of a clinical rating scale (Unified Batten Disease Rating Scale; UBDRS) with standardized training methodology and independent neurological and neuropsychological assessments [20].

The rating scale, modeled after similar scales in adult movement disorders, was designed to assess motor, behavioral, physical, cognitive and overall global function [21, 22]. A preliminary draft of the proposed scale was distributed to acknowledged experts in the field for review, comment, and revision. The URBC began piloting the UBDRS at the BDSRA annual family conference in 2002, which initially served as the primary research setting for conduct of the UBDRS study. The UBDRS study visit consisted of 1) a parent interview by a trained interviewer to capture parent-reported demographics, medical history and medication use, and 2) a physical exam by a neurologist who rated the child's motor function and completed a structured parent-interview regarding seizures, behavior, cognition, and capability; the neurologist also provided a clinical global impression of the child's current disease state.

In the initial years of the study, all subjects were independently examined by three neurologists in order to establish inter-rater reliability of the UBDRS. In subsequent years, duplicate evaluations were completed for the purpose of training new examiners. In the case of children examined previously, an assessment of any change in health since their last examination was also recorded. The UBDRS went through an iterative process over this timeframe to establish meaningful item content. The team collaborated via regular study group meetings to assess the UBDRS performance, relative importance of specific items, and need for revision. Longitudinal follow up of study subjects over a ten-year period at both the annual BDSRA conference and the URBC has enabled refinement of the rating scale and additional lines of inquiry.

To extend the reach of the group's studies to families unable to travel to the annual meeting or to the URBC, the investigators undertook a study to validate the UBDRS physical assessment via telemedicine [23]. The physical assessment is based on direct examination, rather than parent report alone, and thus validation of remote administration of this component specifically was highlighted as of importance.

Neuropsychological Investigations

Investigations of neuropsychological aspects of Batten disease were initiated in 2003 under the direction of the study group neuropsychologist. Initially, a pilot study of attention skills in JNCL was conducted and has expanded into a longitudinal study of the natural history of neurocognitive and behavioral symptoms of JNCL [24, 25]. Parent rating forms completed in person, via telephone, or via mail, were used to assess behavior, psychiatric symptoms, quality of life, and adaptive living skills. Neuropsychological testing was conducted to characterize the neurobehavioral phenotype of JNCL and to provide external validation to components of the UBDRS.

NCL Genotyping

In collaboration with the ongoing NCL investigations in the laboratory of David Pearce PhD, University of Rochester (now Sanford Health, Sioux Falls, IA), where investigations of the molecular basis of JNCL were underway, the UBDRS study protocol was expanded in 2002 to include blood sampling. Beginning in 2004, buccal epithelial cell collection for genotyping as a non-invasive, child-friendly method was used to confirm the genetic status of UBDRS subjects who had not been previously genotyped. These samples were analyzed in the Molecular Diagnostics Section of the University of Rochester Medical Center Clinical Laboratories. A rapid diagnostic testing methodology for the most common *CLN3* mutation, a 965 bp deletion of exons 7 and 8, was developed and validated [26]. For those negative for the common deletion, the entire *CLN3* coding region was subjected to Sanger nucleotide sequence analysis.

Clinical Trial Design and Implementation

Collaboration with the Pearce laboratory led to development of a controlled phase II trial for children with JNCL, entitled "Cellcept for Treatment of Juvenile Neuronal Ceroid Lipofuscinosis" (ClinicalTrials.gov identifier: NCT01399047). The study is funded by the Food and Drug Administration (FDA) Orphan Products Grants Program and the BDSRA. The trial is a randomized, double-blind, placebo-controlled, crossover study of the safety and tolerability of short-term (8-week) exposure to oral mycophenolate in ambulatory children with JNCL. This study will also assess the feasibility of conducting controlled clinical trials in this rare neurological disorder based on novel collaboration between a national center of excellence in the disease (URBC) and participants' local care providers (pediatricians and/or local neurologists). The contact registry was used to obtain parental input regarding specific aspects of trial design, including feasibility of travel for the purpose of clinical trial participation, and also to recruit for the trial.

Results

Batten Registry

One hundred ninety-eight (198) families representing 237 NCL-affected children enrolled in the patient registry between 2001 and 2012. By parent report, JNCL (*CLN3*), was the most common of the NCLs, was reported for 149 children (62.9%); other NCLs or unknown diagnoses were reported as follows: *CLN1* - 23 (9.7 %), *CLN2* - 44 (18.6%); *CLN4* – 3 (1.3%); *CLN5* – 3 (1.3%); *unknown* - 12 (5.1%); *not reported* - 3 (1.3%). Among these, 120

children from 99 families have enrolled in the UBDRS study since 2002 at the BDSRA Annual Conference, the URBC and other locations, such as extending the mobile research setting to home visits or another medical office setting (Table 1). Since its inception, the registry has been used to contact and enroll families for a diverse set of Batten-related projects, including studies of socio-demographic status, visual aid skills utilized by children, attitudes and knowledge about genetic testing, and most recently, to survey families about their interest in participating in a Phase II safety and tolerability clinical trial [27, 28].

UBDRS

The final form of the UBDRS includes: a 20-item Physical Assessment (speech, vision, tone, strength, abnormal involuntary movements, coordination, gait, postural stability), 12-item Seizure Assessment (seizure type, frequency, duration, post-ictal period, frequency of injury, level of care, and recent anticonvulsant adjustment), 10-item Behavioral Assessment (mood, aggression, anxiety, repetitive behaviors, medication use), and a 10-item Capability Assessment (home care level, academic setting, ability to perform activities of daily living and age-appropriate tasks). The Physical Assessment is based on direct examination; the remaining items are based on parent report. Capability is assessed based on the current clinical state, and again under the assumption of normal visual acuity. A Clinical Global Impression (1–5 Likert scale) is applied by the examiner to each subscale and also to the overall clinical state.

There is evidence of convergence of the related constructs Physical and Capability subscales, and divergence of the unrelated constructs Physical and Behavioral subscales [29]. The Behavioral Assessment was further examined through cross-validation with the Child Behavior Checklist, an independently validated, commonly used measure of childhood behavior problems [24]. Appropriate convergence of these measures was demonstrated. The UBDRS demonstrates good inter-rater reliability as measured by intraclass correlations for the Physical, Behavioral, and Capability Assessments – 0.83, 0.68, and 0.85, respectively [20]. This has improved further with refinement of training and experience of the research group. As a reliable and valid instrument to 12 measure disease progression, the UBDRS is a valuable tool for use in clinical trials [30]. High inter-rater reliability of the Physical Assessment administered via telemedicine, as measured by intraclass correlation 0.94, has also been demonstrated [23].

Table 1 summarizes UBDRS study enrollments by year of initial visit and diagnosis. Of 120 subjects evaluated with the UBDRS at least once, 98 presented with clinical features consistent with JNCL. In the clinical JNCL group, 93 (94.9%) of these were confirmed to have *CLN3* mutations. Table 2 describes the number of serial UBDRS exams completed and subject diagnoses for the natural history study. Other NCLs noted include those determinable by genotyping methodology. Subjects noted in either table as ‘undiagnosed’ represent those without a confirmed diagnosis and with a phenotype that was judged to be atypical for an NCL. Disease burden and rate of progression have been evaluated and quantified from the UBDRS data in 82 subjects with genetically confirmed JNCL, representing the largest cohort of Batten-disease patients reported to date using a disease-specific rating scale [29].

Neuropsychological Investigations

Neuropsychological test data have provided quantifiable measures of neurobehavioral function, permitting objective assessment of change in these symptoms over time [31]. In an initial pilot study of cognitive function in JNCL, we evaluated attention skills in 15 affected children. Subsequent investigations have expanded the neuropsychological battery to include tests of attention, memory, verbal fluency, vocabulary, as well as assessments of

quality of life, adaptive skills, and behavioral function. Altogether, 95 children (62 Batten-affected children and 33 siblings) have participated in the neurobehavioral studies. Fifty eight Batten-affected children who enrolled in the neurobehavioral studies also 13 participated in the UBDRS project. Children with JNCL develop significant impairments in attention, memory, verbal fluency, and declines in overall intellectual abilities [25]. Neuropsychological impairment and impairments in adaptive living skills are correlated with disease duration [25, 31]. To date we have not found a significant genotype-phenotype association with respect to either cognitive or behavioral symptoms in JNCL [24]. However, there are preliminary data suggesting there may be sex differences in the rate of disease progression, with females exhibiting a more precipitous disease course with respect to both physical and cognitive symptoms [32]. Cognitive and behavioral symptoms, independently evaluated with established and well-validated neuropsychological measures, have also been used to cross-validate the UBDRS, thus demonstrating that this JNCL disease-specific measure can reliably and validly assess these symptoms [24].

NCL Genotyping

For subjects without a prior genetic diagnosis, genetic confirmation of *CLN3* mutation was performed by first analyzing for the common deletion which accounted for about 85% of the total mutation load and then sequencing the entire coding region in those patients who were not homozygous for the common deletion. Most of the genotyping was done using DNA derived from buccal specimens. In total, 58 patients were homozygous for the *CLN3* common deletion, 23 were compound heterozygotes for the common deletion and another *CLN3* mutation, and one patient had two *CLN3* mutations that did not include the common deletion. Most of the mutations were in the NCL Mutation Database [33]. Several novel mutations have been identified through this process [29, 34].

Further studies

Several additional research questions have been posed to the UBDRS and associated databases (demographics, genotyping results). A number of projects have been initiated based on anecdotal parent reports, including an investigation of the perceived benefit of flupirtine for affected children, sex differences in JNCL symptom onset and rate of progression, seizure characteristics and treatments [32, 35, 36].

Discussion

When the URBC began its clinical research activities, there were no therapies imminently ready for human study. The URBC began preparatory infrastructure development and clinical research in anticipation of future trials, with the hope of adding efficiency and specificity to future studies. Since its initial planning meeting in 2001 with the BDSRA, the URBC has been successful in developing a registry of families interested in future research and recruiting research participants. By offering a mobile research setting at the annual family conferences, the burden of travel is substantially reduced. Families that are able to travel to the URBC can obtain clinical consultation, genetic testing, and participate in clinical research studies. Grant funding (R01NS060022) has subsidized travel expenses to the UBRC for the Batten-affected child(ren) and an accompanying parent. The BDSRA awarded the “Batten Center of Excellence” status to the URBC in 2010 and continues to provide organizational and grant-funding support for the URBC’s mobile and on-site research activities. The URBC has received federal and foundation funding to implement its first randomized, controlled therapeutic clinical trial, which is underway (http://clinicaltrials.gov/ct2/show/NCT01399047) [28].

While the core activities of the URBC were conducted to gather initial data for development and implementation of a future clinical trial, other data collection, while not specifically informing the clinical trial development, has expanded knowledge about Batten disease.

Many different projects and lines of inquiry beyond those discussed have emerged from the initial work of the URBC investigators and collaborations with parents which led to a number of investigations based on their questions and observations. Some studies were based on analysis of the existing data set, but some studies generated original data via new surveys and interviews, demonstrating the utility of the contact registry. The research activities that began in 2002 provided the investigators with more experience and contact with NCL-affected families than most clinical researchers might experience, given the rarity of the NCLs. As a consequence, the URBC was expanded to offer clinical services via its combined diagnostic and clinical research center. The URBC's research interests extend beyond the affected child to the parent, siblings and caregivers. The URBC has disseminated research findings through manuscripts for publication. In addition, via an IRB-approved protocol for data sharing, elements of the UBDRS data are integrated with the National Institutes of Health and the Office for Rare Diseases Research-funded Lysosomal Disease Network/Rare Diseases Clinical Research Network.

Work continues to further characterize the neurobehavioral phenotype of JNCL, and we aim to establish a cohort of at-risk, but as yet unaffected younger siblings for comparison purposes. We have established the feasibility of forming an observational cohort and continued engagement in a rare disease. The URBC hopes to pursue funding and infrastructure support to further develop its registry of Batten affected children and their families.

An inherent limitation in research on rare diseases is the small sample size and the geographical dispersion of affected individuals. Longitudinal follow up of advanced stage subjects is difficult because the effects of the disease limit ability to travel. One of the strengths of telemedicine is that it can address this limitation in part.

The annual BDSRA meetings provide the opportunity to interact with a relatively large group of families at one time, but the cohort of JNCL is a sample of convenience, based on which families attend the conference. A selection bias is possible, due to factors beyond the control of the research group, such as the economy, location, or disease status of affected children. To address this potential bias, we are expanding our telemedicine approach to broaden our outreach to individuals in more advanced stages or remote locations. UBDRS training materials are in development for dissemination to other child neurologists and study groups for use. Similarly, in terms of assessment of the disease in early stages, ongoing educational efforts are underway to improve early recognition of the disease, such as the recent Neurobiology of Disease Symposium focused on Batten Disease held in conjunction with the 2012 Child Neurology Society Meeting.

With the aid of the Batten registry, the URBC has successfully identified individuals who are willing to consider participation in current and/or future research efforts and subsequently enroll into observational and neurobehavioral studies. While enrollment in the registry included children with any NCL, the URBC's primary focus to date has been on juvenile NCL. While the Batten patient registry is currently limited to tracking contact information for recruitment purposes, expansion of the registry and outreach to JNCL-affected families will be a future endeavor of this study group, including collaborations with recently emerging Batten Centers of 17 Excellence, similar to the approach taken by the long-standing Cystic Fibrosis Patient Registry (E. Knapp, personal communication, April 17, 2013).

Lessons Learned

We recognize the importance of the patient advocacy-family-researcher relationship as it relates to recruitment, determination of meaningful clinical outcomes, and development of research questions. Early establishment of the requisite infrastructure will facilitate the initiation of clinical trials. When embarking upon a longitudinal project, all future desired elements cannot be anticipated and evolution of collected measures is likely. In these cases, it is important to have flexibility in the data collection processes, including the actual data structures, which allows for adapting to any new elements or methods while maintaining the integrity of the previously collected information. Data management and biostatistical support are absolutely essential.

Our progress thus far can be attributed in part to innovations, such as enabling access to the research activities via the mobile research lab and telemedicine. The first randomized, controlled phase II clinical trial in JNCL by this group has been launched, with recruitment and enrollment underway. Innovations in study design include our collaboration with parents and patient advocates, as well as with primary care physicians who have been engaged to conduct local study visits to help monitor subject safety in-between protocol visits, for which subjects and families travel to the URBC.

Our productivity to date reflects the feasibility of establishing a cohort and conducting observational studies in a rare childhood disease, prior to identified agents to study in a clinical trial, through partnership of families, researchers, and advocates. Although our work is focused on Batten disease, this research process applies broadly to many rare diseases.

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Abbreviations

BDSRA	Batten Disease Support and Research Association
JNCL	Juvenile neuronal ceroid lipofuscinosis
NCL	Neuronal ceroid lipofuscinosis
NIH	National Institutes of Health
UBDRS	Unified Batten Disease Rating Scale
URBC	University of Rochester Batten Center

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Table 1

UBDRS Study Enrollments by Year of Initial Visit and Diagnosis

			New Subject Diagnoses		
Year	**Total Number of Subjects Evaluated**	**Number of New Subjects Enrolled**	**Clinical JNCL**	**Other NCL**	**Undiagnosed**
2002	22	22	20	0	2
2003	20	10	10	0	0
2004	19	8	3	4	1
2005	37	18	13	4	1
2006	33	13	13	0	0
2007	28	5	4	1	0
2008	43	4	11	2	1
2009	40	16	14	1	1
2010	32	5	2	3	0
2011	26	7	7	0	0
2012	19	2	1	1	0
Total	323	120	98	16	6

Table 2

Subjects by Number of UBDRS Exams and Diagnosis

	Diagnosis		
Annual UBDRS Exams (Total Number of Subjects)	**Clinical JNCL**	**Other NCL**	**Undiagnosed**
1 (63)	49	10	4
2 (16)	12	3	1
3 (11)	11	0	0
4 (7)	5	1	1
5 (3)	3	0	0
6 (7)	5	2	0
7 (5)	5	0	0
8 (2)	2	0	0
9 (2)	2	0	0
10 (3)	3	0	0
11 (1)	1	0	0
Total Subjects	98	16	6
Total Exams	281	32	10