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A Case-controlled Investigation of Pain Experience and Sensory Function in Neuronal Ceroid Lipofuscinosis

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Abstract

Objectives—This case-control study explored pain experience and expression among individuals with Neuronal Ceroid Lipofuscinosis (NCL) through parental report, tactile-sensory testing, and infrared thermography (IRT).

Methods—Individuals with NCL ($n=8$; M age = 14.8 years) and their unaffected siblings ($n=8$; M age 23.5 years) were characterized in terms of pain response to a brief tactile sensory test (light touch, Von Frey monofilament). During sensory testing, behavioral expression was measured using the Battens Observational Pain Scale (BOPS) and infrared thermography (IRT) was used to quantify changes in skin/eye temperature.

Results—Individuals with NCL experienced pain frequently and from multiple sources that negatively impacted their lives. Individuals with NCL were reactive to the sensory testing as indexed by significant increased IRT temperature change ($p<.001$). Across combined sensory conditions, individuals with NCL were significantly more reactive (BOPS total score) to sensory testing compared to siblings ($p<.05$). Similarly, IRT difference scores between sensory conditions revealed a significant increase in temperature for individuals with NCL compared to siblings ($p<.001$).

Discussion—Ongoing reported pain was a problem for the individuals with NCL in this sample. Increased pain expression during the repeated Von Frey filament suggests that the pathophysiology of the ongoing pain may be centrally mediated.

Keywords

Neuronal Ceroid Lipofuscinosis; Batten disease; pain; central sensitization; sensory test

The neuronal ceroid lipofuscinoses (NCL) are a rare group of fatal neurodegenerative brain diseases.¹ The most common form of NCL is Batten disease. These autosomal recessive lysosomal storage diseases are marked by the accumulation of autofluorescent

lipopigments in the brain and throughout the body.² NCL is associated with widespread neuron loss, glial activation, and synaptic pathology which contribute to the devastating clinical presentation of the disease (i.e., blindness, epilepsy, dementia) and ultimately death.^{1,2}

Although there is limited scientific documentation of the pain experience of individuals with NCL, there is reason to suspect that persistent pain may be a problem based on the symptoms associated with the disease (e.g., spasticity, gastrointestinal complications).³ In two survey studies 9 out of 42 and 8 out of 35 parents reported that their child experienced persistent pain.^{4,5} Mannerkoski found that the use of transdermal fentanyl patches reduced persistent pain of central origin in five young children with infant (I)NCL.³ Unfortunately, diagnosing pain and providing effective treatment can be especially problematic when language abilities are compromised as in the case of individuals with NCL during disease progression.^{1,3}

One approach to quantitatively investigate pain experience in communicatively compromised children may be by pairing proxy-report via rating scales developed for use with nonverbal populations with adapted quantitative sensory testing procedures. Proxy report may help to elucidate the perceptions from primary caregivers about the nature of their child's pain or discomfort and calibrated stimuli may be used as an indirect noninvasive method to interrogate the integrity of the peripheral and central nervous system through the individual's ability to detect different stimuli.⁶ Although sensory testing (to our knowledge) has not previously been conducted in the NCL population, there has been some, albeit limited, research demonstrating the efficacy and feasibility of this approach for documenting tactile and nociceptive sensory capacities of other populations with neurological impairments and limited communication abilities.^{7–10}

Considering the degeneration of the central nervous system and the neuronal damage known to occur during the progression of NCL¹ and two prior survey studies, there is ample reason to speculate about sensory problems in relation to the possible pain experienced as the disease progresses.⁴ Accordingly, the purpose of this study was to extend the prior survey study findings by 1) further evaluating the use of pain scales developed from work with nonverbal children with developmental disabilities to characterize the pain experience of individuals with NCL, and 2) testing the feasibility of a non-invasive approach for quantifying sensory reactivity among individuals with NCL.

Materials and Methods

Sample Characteristics

Following IRB approval, a convenience sample of 8 individuals diagnosed with NCL (4 male; M age = 14.8 years, SD = 4.66, range = 8–22) was recruited through a national family NCL conference. Parents provided written informed consent for all participants with NCL and siblings under the age of 18. Siblings over age 18 provided their own written informed consent. One participant was diagnosed with late infantile NCL and seven with juvenile NCL. All participants lived at home with their families and six were currently attending school. Motor capacity was assessed using the parent version of the Gross Motor Function

Classification System (GMFCS; levels I–V).¹¹ Participants with NCL could ambulate without assistance (level I; $n=1$), could ambulate with some assistance (level II; $n=2$), were non-ambulatory but self-mobile in a wheelchair (level IV; $n=1$), and were non-ambulatory and reliant on others for wheeled mobility (level V; $n=3$). The verbal abilities of participants with NCL included the ability to use conversational language (e.g., could tell stories; $n=3$), the ability to use single words and signs ($n=1$), and no ability to use words or signs ($n=2$). Participants with NCL had seizures ($n=6$), vision impairment ($n=7$), musculoskeletal challenges (e.g., spasticity, muscle spasms; $n=5$), constipation ($n=4$) and G-tube placement ($n=1$). A list of the medications participants were taking at the time of the study is displayed in table 1. A comparison group consisted of siblings either unaffected by NCL ($n=2$) or were known to be NCL carriers ($n=6$, 2 male; M age = 23.5 years, $SD = 9.13$, range = 8–37). The sibling comparison group did not exhibit any signs or symptoms of NCL.

Measures

Parents completed questionnaires related to the health and pain status of their child with NCL ($n=7$; one questionnaire was not returned).

The Batten's Observational Pain Scale (BOPS) was used as a measure of parent's recall of pain behaviors demonstrated by their child with NCL in the previous week.¹² The BOPS was derived from the Non-Communicative Children's Pain Checklist – Revised (NCCPC-R) and specifically adapted for individuals with NCL. In the initial validation BOPS scores significantly correlated with the visual analogue scale of pain for the same observation times ($r = .57$). The BOPS showed strong sensitivity (92%) and specificity (89%) to pain behaviors. The cut off scores were determined to be 4 (pain is present), 7 (moderate pain is present), and 23 (severe pain is present).¹² In this sample the BOPS showed strong internal consistency (Cronbach's $\alpha = .92$).

A pain questionnaire was adapted based on a questionnaire previously used for eliciting pain information from study samples with X-linked neurodevelopmental disorders including Rett syndrome¹³ and Fragile X syndrome.¹⁴ Specifically, responses were elicited for overall frequency of pain, pain types, and the pain intensity of each type of pain reported in the previous month (scored 0–10).

The Brief Pain Inventory (BPI) was used to determine the extent to which pain interfered with daily life in the previous week.¹⁵ For the BPI parents report the extent that pain has interfered with activities such as sleeping, communication, and mobility in the previous week. Parents rate the extent of pain interference from 0 meaning “does not interfere” to 10 “interferes completely”. Previously, the BPI has shown excellent internal consistency (Cronbach's $\alpha = .89$) and strong correlation with pain intensity ratings when reported by adults with cerebral palsy ($r = .66, p < .01$).¹⁵ The BPI has also been used as a parent proxy report tool for children with cerebral palsy and duration of pain was significantly related to BPI total score ($p < .05$).¹⁶ In this sample the BPI showed strong internal consistency (Cronbach's $\alpha = .96$) and significantly correlated with parent reported pain intensity ratings ($r = .76, p < .05$).

Participants in both groups (NCL, siblings) experienced a brief tactile sensory test to determine the extent to which they were sensitive and reactive to two forms of tactile stimuli. The sensory test included a light touch with a cotton swab on the palms, forearms, shins, and top of the feet. The second test was a 60g Von Frey monofilament touched repeatedly to two body locations at 1 Hz for 30 seconds. This test of temporal summation (i.e., increased pain perception to a repetitive stimulus) was used as a partial test for central sensitization (i.e., sensitization of the central nervous system resulting in amplified pain signaling).^{17,18} The two body locations were 1) the front of the wrist and 2) the mid to upper portion of the trapezius muscle. These locations were chosen in part, because they were accessible on every participant regardless of clothing, wheelchair use, contractures or braces. Multiple research protocols have specified the use of the palm as well as the trapezius muscle which has been shown to be useful for detecting deep muscle pain as well as chronic musculoskeletal pain.¹⁹ Palms were often inaccessible due to contracture of the hand; thus, the front of the wrist was chosen because it was in close proximity to the palm, is also glabrous skin, and this site ensured consistency in location across participants.

The BOPS was used to quantify pain behaviors (i.e., moaning, tears, furrowed brow) directly observed from video that was recorded just prior to the first stimulus application (light touch) and ended just after the last stimulus application was completed (repeated von Frey).¹² The 17 pain behavior items on the BOPS were coded 0 “not at all”, 1 “just a little”, 2 “fairly often” and 3 “very often”. The scores for each item were summed to create a total score for the time period associated with each sensory test for each participant. A portion of the videos (~ 28%) were coded by a second observer to ensure accuracy. The mean inter-observer agreement (IOA; calculated as the number of agreements/total number of items) between the two coders was 92.8%.

Infrared thermography (IRT) was used as an exploratory approach to quantify changes in eye and face temperatures to indirectly characterize changes in autonomic function during the sensory testing. IRT was collected using a FLIR T400 IRT camera held approximately 50 cm from and orthogonal to the participant’s face. The methodology for analyzing the IRT data was based on the methods used by previous IRT non-human research.²⁰ The temperature of the skin surrounding each eye was collected for 1) a point directly above the eyebrow toward the midline of the face, and 2) a point associated with the tear duct on the inside corner of the eye. The temperature of each entire eyeball was collected in the form of 1) the average temperature of the ellipse associated with the eyeball and 2) the maximum temperature within the ellipse associated with the eyeball. Total body temperature was taken using a standard ear thermometer to determine if baseline body temperature differed between groups.

Statistical Analysis

Data were analyzed using SPSS version 19 (SPSS Inc, Chicago IL, USA). Descriptive statistics were generated, as appropriate, to characterize pain intensity, frequency, type and interference with daily life. Two outcome measures were used (BOPS, IRT) to determine whether individuals with NCL and siblings were reactive to the two types of sensory stimuli (light touch [baseline], repeated Von Frey monofilament test [partial test of central

sensitization]). BOPS total scores (observational measure of pain expression) were calculated for each participant during the light touch condition and the repeated Von Frey monofilament condition. A repeated measures *t*-test was conducted to determine if the change in BOPS scores were significant from one sensory test to the other. IRT data were analyzed first by calculating mean temperature scores for each IRT site on the face and eyes. A repeated measures *t*-test was conducted to determine if the change in IRT temperature at each site was significantly different. One participant with NCL was excluded from repeated measures IRT analyses because movement artifacts resulted in no usable data for the light touch condition. Five participants had movement artifacts affecting a portion of the eight possible IRT sites across the two conditions. Thus, 18 of 240 IRT temperatures were replaced by mean temperatures for that IRT site from participants of the same group (NCL, sibling).

To compare sensory reactivity between groups (NCL, sibling comparison group); first, an independent samples *t*-test was conducted to determine if individuals with NCL were more or less reactive (BOPS) across both sensory testing conditions (light touch, repeated Von Frey) combined compared to the sibling comparison group. Second, difference scores were calculated for both outcome measures (BOPS, IRT) to determine if individuals with NCL reacted differently to each sensory stimuli (light touch, repeated Von Frey) compared to the sibling comparison group. Finally, independent samples *t*-tests were conducted to determine if the difference scores of each outcome measure (BOPS, IRT) were significantly different between the two groups (NCL, sibling).

Results

Pain Experience of Individuals with NCL

The types of pain experienced by individuals with NCL and the associated pain intensity (scored 0–10) are displayed in table 2. Parents reported that their child with NCL experienced pain about once a week ($n=3$), almost every day ($n=2$), and every day ($n=2$). Pain interfered most with enjoyment of life (scored 0–10; $M=2.86$, $SD=4.02$), mood ($M=2.71$, $SD=3.30$), sleep ($M=2.43$, $SD=3.40$), and social abilities ($M=2.43$, $SD=3.55$). Based on the cut off scores established for individual total BOPS scores¹² (based on a 1-week recall), there was a 94% chance that 5 participants were experiencing moderate pain, and an 80% chance that one participant was experiencing severe pain in the previous week.

Differences in Pain Reactivity between Groups

Seven participants with NCL had elevated BOPS scores during the light touch condition and five of those participants showed an increase in pain behavior during the repeated monofilament stimulus condition (Table 3). The sibling comparison group showed very few pain behaviors across sensory conditions. Across combined conditions (light touch, repeated Von Frey), individuals with NCL were significantly more reactive (BOPS total score) to sensory testing ($M=11.75$, $SD=10.21$) compared to the sibling comparison group ($M=1.25$, $SD=1.49$; $t(7.30)=2.88$, $p<.05$) with 95% confidence intervals (CI) of (3.22, 20.28) and (0.01, 2.49) respectively. The mean BOPS scores observed during each sensory testing condition for the participants with NCL and siblings are depicted in Figure 1. The difference

scores between conditions did not differ significantly between participants with NCL ($M=2.75$, $SD=5.20$) and siblings ($M=0.25$, $SD=1.60$) ($t(14)=1.17$, $p=.26$) with 95% CIs of $(-1.60, 7.10)$ and $(-1.15, 1.65)$ respectively.

For the NCL group the mean temperatures for all IRT sites (above eye brow, tear duct, eye maximum, eye average) on both the left and right sides significantly increased from the light touch to the repeated Von Frey condition whereas for the sibling group the mean IRT temperatures on both sides decreased. The mean IRT temperatures for each IRT site are depicted in Figure 2. The difference scores between the two conditions for all IRT sites were calculated for the participants with NCL ($M=1.09$, $SD=0.46$) and siblings ($M=-0.09$, $SD=0.23$) and were significantly different ($t(14)=6.55$, $p<.001$) with 95% CIs of $(0.71, 1.48)$ and $(-0.28, 0.09)$ respectively. The total body temperature (measured with a standard ear thermometer) of individuals with NCL ($M=97.6$, $SD=0.93$) did not differ from the sibling comparison group ($M=97.8$, $SD=0.99$; $t(14)=-0.36$, $p=.72$) with 95% CIs of $(96.86, 98.42)$ and $(96.99, 98.64)$ respectively.

Discussion

The results indicate that individuals with NCL are considered by their parents to experience pain from multiple sources (musculoskeletal, gastrointestinal, headache, daily living pain) and with significant intensity. These results are consistent with two prior NCL surveys^{4,5} but provide more detailed information on the nature of the pain experience. Pain was severe enough to interfere with daily activities. The BOPS scores demonstrated that individuals with NCL do show observable signs of pain that can be quantified. BOPS scores calculated based on a one-week parent recall were above the cut-off score for moderate or severe pain for six of the seven participants for whom the BOPS was completed. Further, BOPS scores were elevated during the light touch portion of the sensory test. This suggests that individuals with NCL in this sample may be living with ongoing pain that has not been well controlled. BOPS may be a useful measure for caregivers and healthcare providers to determine when an individual with NCL is in pain and provide a rationale for analgesic management.

Combined pain expression (BOPS) scores across both sensory tests (light touch, repeated Von Frey) demonstrated that individuals with NCL were significantly more reactive to tactile stimuli compared to the sibling comparison group. The observed elevated sensitivity in response to tactile stimuli may be considered an indicator that the peripheral and central circuitry for transducing and transmitting somatosensory relevant information was intact in the NCL sample. This evidence opposes the perspective that individuals with cognitive limitations are insensitive or unresponsive to tactile sensory or noxious stimuli.²¹ Other recent research studies investigating tactile sensory testing have also demonstrated directly observable responsiveness in other cognitively impaired populations.^{9,10}

The repeated Von Frey monofilament was used as a partial test of temporal summation; i.e., increased pain perception to a repetitive stimulus.^{17,18} Based on the BOPS scores, individuals with NCL in the sample showed greater reactivity to the repeated Von Frey monofilament compared to the sibling comparison group. For four individuals with NCL the

BOPS total score during the repeated Von Frey test was great enough (>4) that the individual would be considered to be in pain according to the cut off scores for the BOPS. This was somewhat surprising given that the 60g monofilament is not typically considered a nociceptive stimulus. The increased reactivity is consistent with a response mediated by central sensitization.^{17,18}

Response differences between the NCL and sibling comparison group were also observed for the IRT biomarker data. The IRT application was an exploratory aim of the study. The NCL children showed a significant increase in temperature on all face and eye IRT sites during the repeated Von Frey monofilament. Increased eye temperatures have been documented using IRT in animal models of pain.²⁰ Although the mechanisms underlying the temperature changes are not currently well understood, it appears that IRT may be a useful method of quantifying surface temperature changes associated with increased or decreased blood flow in the superficial capillaries surrounding the eye that are under autonomic nervous system control.

The increased pain expression and change in autonomic function during the repeated application of the Von Frey filament further suggests that the pathophysiology of the ongoing pain reported for the individuals with NCL was likely centrally not peripherally mediated.^{19,22} This finding is consistent with a prior case series report documenting analgesic response to fentanyl for central pain in an infant sample.³ Recent research in animal models²³ and human post mortem analyses²⁴ suggests that glial activation and synaptic pathology (and not accumulation of lipopigments) are predictive of neuron loss in NCL. More specifically, the biology of astrocytes and microglia seem to be compromised in NCL and could therefore be responsible for the degradation of neurons.³ Given this, it may be highly relevant that astrocytes and microglia are routinely activated during spinal nociceptive transmission and central sensitization.²⁵ This involvement is considerable, such that when glial cell activation is blocked the development of allodynia and hyperalgesia is delayed or prevented.²⁶ The recent research specifically associating microglia and astrocytes with central sensitization has only been conducted in animal models; however, the basic science provides insight into the possibility that glial activation associated with the natural course of the disease may predispose individuals with NCL to develop pain of central origin. As such, glial cells and their products may be possible therapeutic targets.

The data presented here are not confirmatory but are preliminary and descriptive and intended only to provide the first steps toward characterizing pain experience and potential sensory differences in individuals with NCL. For example, it is unknown whether differences in age and visual ability between groups may have influenced the results. Participants were recruited via convenience sampling which limits the generalizability of the results presented. This study provides another application of the BOPS which was derived from a validated scale (NCCPC-R)²⁷ but requires further application in this population to establish reliability and validity beyond the initial test group.¹² IRT was used in a preliminary way to identify possible changes in autonomic function; however, the mechanisms underlying the changes demonstrated in this study are not well understood.

This study used a novel approach to quantify pain experience and expression and sensory reactivity for a complex patient population for whom self-report is unreliable due to cognitive and language limitations.^{7–10} However, the sensory testing approach as described may not be clinically practical. But, the results are clear that clinicians and caregivers should consider that individuals with NCL may experience a great deal of pain that possibly worsens with the progression of the disease. The pain may be chronic and of a central rather than peripheral origin, making treatment more challenging. The BOPS may be used to identify and measure pain and determine the effectiveness of treatment approaches to improve comfort for individuals with NCL.

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Figure 1.

Mean BOPS scores depicting pain expression in each of the two sensory testing conditions (light touch [LT], repeated Von Frey [RVF]) are shown for individuals with NCL, and the sibling comparison group. Across combined conditions (light touch, repeated Von Frey), the NCL group was significantly more reactive (BOPS total score) to sensory testing ($M=9.25$, $SD=9.17$) compared to the sibling comparison group ($M=1.25$, $SD=1.49$; $t(7.37)=2.43$, $p<.05$).

Figure 2.

Mean IRT temperatures for each IRT site during each of the two sensory testing conditions (light touch [LT], repeated Von Frey [RVF]) are shown for children with NCL, and the sibling comparison group. The difference scores between the two conditions for all IRT sites were calculated for the NCL group ($m = -2.00$, $SD = 0.97$) and sibling group ($m = 0.13$, $SD = 0.26$) and were significantly different ($t(14) = -5.98$, $p < .001$). Total body temperature (measured with a standard ear thermometer) of NCL group ($m = 97.6$, $SD = 0.93$) did not differ from the sibling comparison group ($m = 97.8$, $SD = 0.99$; $t(14) = -0.36$, $p = .72$).

Table 1

Daily medications for participants with NCL.

Participant	Medications
1	Levetiracetam (Keppra), Lamotrigine, Zonisamide (Zonegran), Quetiapine (Seroquel), Baclofen, Fluoxetine (Prozac), Lorazepam (Ativan)
2	Carbamazepine (Carbatrol), Levetiracetam (Keppra), Phenytoin (Dilantin)
3	Clonazepam, Topiramate (Topamax), Levetiracetam (Keppra), Glycopyrrolate
4	Topiramate (Topamax), Levetiracetam (Keppra), Risperidone (Risperdal), Clonazepam, Baclofen, Calcium Carbonate (Caltrate), Vitamin E
5	Levetiracetam (Keppra), Risperidone (Risperdal)
6	No medications
7	Divalproex Sodium (Depakote), Quetiapine (Seroquel), Clonidine, Ubiquinone (Coenzyme Q10), Vitamin E

Table 2

Parental endorsement of pain type and intensity (n=7).

Pain Type	Number of participants experiencing pain type (n=)	Median Intensity (0–10)
Musculoskeletal pain	5	6.5
Gastrointestinal pain	5	6.5
Headache pain	4	2
Everyday pain	4	1
Seizure pain	2	3.5
Equipment related pain	2	3.5
Daily living	2	4

Table 3

Mean scores for sensory testing conditions between NCL and Sibling comparison groups

	Light Touch M(SD)	Repeated Von Frey M(SD)	Significance
NCL Group (n=8)			
BOPS scores	4.5 (4.41)	7.25 (6.80)	$P = .18$
IRT temperatures	91.57 (1.24)	92.67 (1.09)	$P < .001$
Sibling Group (n=8)			
BOPS scores	0.38 (0.52)	0.88 (1.46)	$P = .41$
IRT temperature	96.31 (1.02)	96.22 (0.99)	$P = .28$