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Parent Reported Pain in Rett Syndrome

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Rett syndrome (RTT) is a severe neurodevelopmental disorder caused primarily by mutations in the methyl-CpG-binding protein 2 gene (*MECP2*) affecting predominantly females. Neurodevelopmentally, the syndrome is characterized by apparently normal pre- and perinatal development, normal head circumference at birth, deceleration of head growth between 5 months and 4 years of age, loss of acquired purposeful hand skills followed by the development of stereotypical hand movements, severe impairments in expressive and receptive language, and gait apraxia.¹ RTT is also associated with a number of health problems including scoliosis, seizures, cardiorespiratory dysfunction, and gastrointestinal issues.^{2,3}

The scientific knowledge base concerning the clinical problem of pain among patients with RTT is limited and presents somewhat of a paradox. On the one hand, there are numerous health issues, many of them chronic (e.g., constipation, scoliosis), for which it would be reasonable to raise the index of suspicion regarding the possibility of recurrent and chronic pain, particularly among a vulnerable population with communicative, motor, and intellectual impairments. But, on the other hand, there is an apparent pain insensitivity or indifference reported among providers and caregivers and made clear by Hagberg's description of the paradoxical case of a girl with RTT laughing while her hand was exposed to a candle flame.² Atypical pain responses and apparent pain insensitivity are considered part of the supporting diagnostic criteria in the delineation of variant phenotypes ("diminished response to pain")¹ and also described and discussed as evidence of impaired pain perception or increased pain thresholds despite the fact that there has been no psychophysically-based study specific to pain thresholds among individuals with RTT.^{4,5}

The sum total of the scientific evidence from empirical work explicitly addressing pain among RTT is based on three studies.^{6,7,8} One was a single case report documenting reduced post-operative analgesic requirements following surgical intervention for scoliosis.⁶ Behavioral ratings and maternal impression were consistent and suggested reduced pain (expression). A second was a parent survey in which 81% (51/63) of RTT cases were reported to be insensitive to pain.⁷ The third was a large (N=646) population source based on multi-national registries that included an item or items about altered pain sensitivity as well as the opportunity for open-ended responses.⁸ In this study, the majority of parents reported reduced pain sensitivity with the effect most pronounced among younger cases, although when severity of impairment/disability was controlled for the effects were marginal. For some cases, pain sensitivity was reported as increased. There appeared to be a distinction between 'external' pain (from trauma, falls, accidents, self-injury, etc.) as being reduced but 'internal' pain (from gastrointestinal, etc.) as being increased. There was also

preliminary evidence that genotype mattered with a C-terminal, p.R168X or p.R306C mutation to have reported decreased pain sensitivity.

Collectively, the chronic health issues associated with the syndrome and the numerous adaptive behavior problems related to motor and communication impairments may mean that individuals with RTT are at risk for living with pain but not having it readily recognized. None of the studies reported on to date have used any of the existing pain scales developed for individuals with developmental disabilities. The purpose of this survey was to describe pain (frequency, source) in a small RTT sample specifically using items from the Non-Communicating Children's Pain Scale –Revised (NCCPC-R) pain scale⁹, which had been previously validated on samples with communicative impairments associated with developmental disability.

Methods

Caregivers of 44 girls and woman with clinically diagnosed Rett syndrome completed a health survey about their daughter that contained items specific to pain. Families were recruited by mail (surveys were sent out with a self-addressed stamped return envelope) from existing records with the assistance of a state parent advocacy organization (Minnesota Rett Syndrome Research Association). The health items included yes/no questions regarding whether the individual currently experienced six health issues (sleep problems, scoliosis, appetite problems, seizures, allergies, and sensitivities/paradoxical reactions to medications).

The health-survey's pain items were from the Non-Communicating Children's Pain Checklist - Revised (NCCPC-R)⁹. The NCCPC-R was designed specifically for measuring pain among individuals with impairments (motor, communicative, intellectual) associated with developmental disability. The health questionnaire included additional items related to pain and developmental disability based on prior work from the National Fragile X Survey¹⁰. Specifically, responses were elicited for frequency (About how many days in the past month was your child in pain? 0, 1–2, 3–7, 8–14, 15 or more), severity (How does the severity of your child's pain compare to those of children without disabilities? Less than, about the same as, more than other children), expression (e.g., Does your child typically communicate pain in these ways? Verbally, with changes in motor activity, with changes in facial expression, etc.), and types (e.g., Is your child regularly affected by these types of pain? Gastrointestinal, musculoskeletal pain, etc.).

Results

Thirty-eight mothers (86.4%); three fathers (6.8%) and three foster parents (6.8%) completed the survey. The response rate for the survey was 22% (44/200; the response rate reflects a one-time anonymous survey with no follow up). The mean age of the girls and women with RTT reported on was 21.5 (2–49). Descriptive statistics were used to summarize the survey findings. Spearman's rank correlation coefficients (ρ) were used to examine linear relations between pain and health variables. Of the 44 families responding to the survey, 24% reported that their child had experienced pain on 8 or more days (> 1 week) in the previous 30 days (43% were unsure) (Fig. 1). Ninety percent of the individuals reported on with RTT did not use words for pain. The most frequent form of pain communication was facial expression (85%) and vocalization (82%, e.g., moan, cry). The most commonly reported pain source was gastrointestinal [GI] (66%) (Fig 2). Thirty-two percent of respondents reported that their child's pain experience was less severe compared to other children without disability (14% reported that it was more). Seizures were reported for 46% of the sample, and scoliosis was reported for 59% of the sample. Pain frequency was significantly ($p < 0.05$) correlated (Spearman r) with age ($r = 0.41$), number of pain

sources ($r = 0.72$), and number of health problems ($r = 0.45$); and the number of pain sources was significantly ($p < 0.05$) correlated with number of health problems ($r = 0.67$).

Discussion

The results from this preliminary study suggest that pain was a problem for a significant subgroup of girls and women living with RTT. Our return rate for the entire survey of a little over 20%, although a fairly typical response rate for a 1-time survey with no follow up, suggests caution should be used in considering the results as representative of the population of girls and women with RTT. Given the nature of the syndrome, it is important to note that the results were dependent on proxy report and there are almost certainly poorly understood sources of variability introduced by this approach. Nevertheless, so little work has been done addressing pain among girls and women with RTT that we considered it relevant information because it reflects the perceptions of the parents responsible for their care and comfort. To provide a more standardized approach to eliciting information from parents about their daughter's pain, items from the NCCPC-R were used which we considered a small (albeit limited) step forward from ad hoc single or limited items used in previous survey studies of the RTT behavioral phenotype. Almost one quarter of respondents in this sample indicated their daughters experience the equivalent of over a week of pain per month. Gastro-intestinal reported pain was the most common pain source but the methods used in this inquiry preclude knowing with precision the specific nature of this suspected pain source. Significant relationships were found between pain frequency and age, pain source, and health problems. Of concern was that almost none of the respondents indicated that their daughters used words to communicate about pain. The current 'gold standard' for pain – for clinical and research purposes – still tends to rely on self-report.

From a basic pain science perspective, there may be a complex interaction between nociceptive and inflammatory mechanisms related to untreated pain, its chronicity, and the possibility of activated 'central sensitization' mechanisms contributing to the RTT behavioral phenotype. It has been shown that MeCP2 is phosphorylated in lamina I projection neurons following the induction of peripheral inflammation¹¹. Lamina I neurons are implicated in the development of pain states¹², and thus there is the possibility that MeCP2 also contributes to chronic inflammatory pain states.

From a clinical care perspective, the frequent health issues and communication impairments associated with RTT suggest an increased risk that the problem of pain may be overlooked or discounted in this vulnerable population. Taken together, it would seem prudent that directly addressing the problem of pain in RTT at the bench and in the clinic could lead to more detailed scientific understanding of the possible relation between MeCP2 and inflammation and improve the quality of care received to reduce pain and increase comfort, respectively.

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Figure 1.
Percent of caregivers reporting frequency of pain in the previous month.

Figure 2.

Percent of caregivers reporting pain types. Note: GI = gastrointestinal; TH = therapy (e.g., PT, OT); EV = everyday pain (e.g., bumps, bruises); MU = musculoskeletal; DE = device (e.g., brace, g-tube); DL = daily living (e.g., assisted walking, toileting); SE = seizures; ME = medical/nursing (e.g., injections, surgery); AC = accidental (e.g., injury requiring medical attention)