Pediatric Neurology 75 (2017) 91–95

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Defining Hand Stereotypies in Rett Syndrome: A Movement Disorders Perspective

Marisela E. Dy MD [a,b,c,*], Jeff L. Waugh MD, PhD [a,b,c], Nutan Sharma MD, PhD [a,b,c], Heather O'Leary BS [a,c], Kush Kapur PhD [a,c], Alissa M. D'Gama PhD [c], Mustafa Sahin MD, PhD [a,c], David K. Urion MD [a,c], Walter E. Kaufmann MD, PhD [a,c,d]

[a] *Department of Neurology, Boston Children's Hospital, Boston, Massachusetts*
[b] *Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts*
[c] *Harvard Medical School, Boston, Massachusetts*
[d] *Center for Translational Research, Greenwood Genetic Center, Greenville, South Carolina*

ABSTRACT

INTRODUCTION: Hand stereotypies (HS) are a primary diagnostic criterion for Rett syndrome (RTT) but are difficult to characterize and quantify systematically. **METHODS:** We collected video on 27 girls (2-12 years of age) with classic RTT who participated in a mecasermin trial. The present study focused exclusively on video analyses, by reviewing two five-minute windows per subject to identify the two most common HS. Three raters with expertise in movement disorders independently rated the five-minute windows using standardized terminology to determine the level of agreement. We iteratively refined the protocol in three stages to improve descriptive accuracy, categorizing HS as "central" or "peripheral," "simple" or "complex," scoring each hand separately. Inter-rater agreement was analyzed using Kappa statistics. **RESULTS:** In the initial protocol evaluating HS by video, inter-rater agreement was 20.7%. In the final protocol, inter-rater agreement for the two most frequent HS was higher than the initial protocol at 50%. **CONCLUSION:** Phenotypic variability makes standardized evaluation of HS in RTT a challenge; we achieved only 50% level of agreement and only for the most frequent HS. Therefore, objective measures are needed to evaluate HS.

Keywords: Rett syndrome, hand stereotypies, video analysis, operational definitions, actigraphy

Pediatr Neurol 2017; 75: 91-95

Author Contribution (Roles): Marisela E. Dy: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.A: Writing of the first draft. Jeff L. Waugh: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.B. Review and Critique. Nutan Sharma: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.B. Review and Critique. Heather O'Leary: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique. Kush Kapur: 2A. Design B. Execution C. Review and Critique 3.B. Review and Critique. Alissa M. D' Gama: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique. Mustafa Sahin: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique. David K. Urion: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique. Walter E. Kaufmann: 1.A. Conception B. Organization C. Execution 2.A. Execution C. Review and Critique 3.B. Review and Critique.

Declaration of Conflicting Interests: Walter E. Kaufmann is a consultant to Neuren, Edison, Newron, EryDel, Marinus, Anavex, GW Pharmaceuticals, and Echo Pharmaceuticals. He has received funding to his institution from Novartis, Ipsen, Eloxx, and Neuren. Mustafa Sahin received research support from Roche, Pfizer, Novartis, Neuren. He is also on the Scientific Advisory Board of Sage Therapeutics. The mecasermin trial was supported by Rettsyndrome.org (Grant 2907), the Translational Research Program at Boston Children's Hospital, Boston Children's Hospital Intellectual and Developmental Disabilities Research Center P30 HD18655; the Harvard Catalyst—The Harvard Clinical and Translational Science Center (National Institutes of Health Grant 1 UL1 RR 025758-01); and Ipsen Pharmaceuticals. Nutan Sharma, Jeff L. Waugh, Heather O'Leary, Kush Kapur, and David K. Urion declare that no specific funding was received for this work and that there are no conflicts of interest relevant to this study.

Funding (Financial Disclosure): Marisela E. Dy, M.D. was funded by Rettsyndrome.org under the U54 HD 061222 NIH grant. Alissa M. D'Gama received research support by award Number T32GM007753 from the National Institute of General Medical Sciences. Mustafa Sahin received research support from Roche, Pfizer, Novartis, Neuren. He is also on the Scientific Advisory Board of Sage Therapeutics. Walter E. Kaufmann is a consultant to Neuren, Edison, Newron, EryDel, Marinus, GW Pharmaceuticals, and Echo Pharmaceuticals. He has received funding to his institution from Novartis, Ipsen, and Eloxx. Nutan Sharma, Jeff L. Waugh, Heather O'Leary, Kush Kapur, and David K. Urion have no additional financial disclosures to report.

Ethical Approval: Parents or legal guardians provided informed consent. Collection of clinical videos was approved by the Boston Children's Hospital Institutional Review Board as part of the larger insulin-like growth factor-1 (IGF-1) study.

Article History:
Received April 19, 2017; Accepted in final form May 28, 2017

* Communications should be addressed to: Dr. Dy; 300 Longwood Ave; Fegan 11; Boston, MA 02215.
E-mail address: Marisela.dy@childrens.harvard.edu

0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2017.05.025

Introduction

Rett syndrome[1] (RTT, OMIM #312750) is a neurodevelopmental disorder that typically affects females, although it can rarely occur in males. Patients with RTT develop repetitive hand movements called hand stereotypies (HS), which are a primary diagnostic criterion for RTT.[2-4] The HS in RTT tend to be continuous, include mouthing, mainly midline, and can involve the use of objects.[5] HS may precede the loss of hand function and appear to evolve over time.[6-9] In older individuals with RTT, parkinsonism limits the expression of HS.[3,4,10] It is unknown whether the underlying mechanism driving the stereotypy truly resolves. In addition to HS, patients with RTT have a breadth of other less well-characterized stereotypies that include body rocking and other lower extremity movements.[11,12] Stereotypies in RTT are phenotypically heterogeneous, varying in location, frequency, and severity, making it challenging to assess them systematically. For the purposes of this study, we focused only on HS. The value of categorizing patients with RTT based on their HS may provide insight into the underlying pathophysiology and/or provide prognostic information.

Most studies have characterized HS by direct cross-sectional observations. However, delineations using video analysis have also been reported.[4,11-14] Only one study was a complete blinded review,[5] whereas in another study the initial evaluation was blinded, with subsequent adjustments based on reviewing frequently to ensure consistency.[4] Previous studies have focused on descriptions of the features of the HS, associations with *MECP2* mutations, changes over time, relationship with behavioral abnormalities, and comparison with HS in other disorders.[4,5,14-17] This body of literature highlights multiple methodologic issues. Prior attempts to characterize HS have been made in using either a single rater with a coding system[11,12] or having different raters define their own operational definitions based on video review.[14] In the study with a completely blinded review, the focus was a comparison of HS between individuals with RTT and autism spectrum disorder. In addition, other studies have used categories without clearly defined terms[18]; only a recent study looking at anxiety and HS provided operational definitions of the abnormal movements.[14] We endeavored to develop a protocol for the systematic characterization of HS. Our objective was to better define the types and features of HS in RTT for their systematic assessment in observational and intervention studies.

Methods

Participants

A total of 27 girls with RTT participated in a phase 2 randomized controlled trial with mecasermin (recombinant human insulin-like growth factor-1 (IGF-1); NCT01777542). Clinical assessment with video recording was performed before their first subcutaneous injection of drug/placebo. Trial recruitment and implementation were performed at Boston Children's Hospital. Subjects met the diagnostic criteria for classic RTT,[2] harbored a *MECP2* mutation, and were in the postregression phase.[19] The subjects ranged in age from 2 years 10 months to 11 years 4 months (average age = 6 years 4 months). The most common *MECP2* mutations observed were T158M (n = 5), R133C (n = 5), R294X (n = 4), and R168X (n = 4). Other mutations included R270X, R133P, exon4a-4b del, c.519_522delTAAG, c.140 G>C, c.1163-1197del, c.1157-1200del, and T158M and c.1143_1160del (one subject with each mutation). Parents or legal guardians provided informed consent. Collection of clinical videos was approved by the Boston Children's Hospital Institutional Review Board (IRB) as part of the larger IGF-1 study.

Video analyses and operational definitions

Videotaped recordings were reviewed by three raters (H.O., M.E.D., A.M.D.) to isolate two five-minute periods within each video that included the two most common HS for each subject. Three of the 27 subjects were excluded from the analyses: one subject had a casted arm and two subjects had restrained arms, precluding visual assessment. Table 1 depicts the operational definitions designed by one of the raters (M.E.D.), which included modifications to the operational definitions reported by Quest et al.[14]

Videos were rated according to nominal (initial protocol) categories derived from prior studies (see Table 1).[4,11,12,14-16,20,21] The two most frequent HS seen were labeled as HS1 and HS2. HS1 was the most frequent of the two HS representative in the five-minute window. HS2 was the second most frequently occurring HS within the five-minute window. Poor inter-rater agreement using previously reported categories convinced us that refinement and simplification of these categories was required. The operational definitions were revised based on

TABLE 1.
Operational Definitions of Hand Stereotypies

Clapping	Any instance in which palms of hands come together like someone is applauding. Fingers cannot interlace
Wringing/washing/clasping	Proposal for spectrum: requires that both hands are involved in the movement (A) Wringing/washing: any instance in which hands/fingers are interlaced with wrist rotation (B) Clasping: any instance in which fingers are interlaced
Squeezing/clenching	Proposal for spectrum: can be unilateral or bilateral. (A) Squeezing: any instance in which the hands open and close repetitively to make a fist. (B) Clenching: any instance in which the hands make a fist
Flapping	Any instance in which arms/wrists make a back-and-forth movement. Can be unilateral or bilateral
Mouthing	Any instance in which any part of fingers or hands are in the mouth This can include nail biting/finger licking. Can be unilateral or bilateral
Tapping	Any instance in which there is repetitive contact made with fingers or palm on a surface or on chest
Mixed midline hand movements	Any instance in which each hand is involved in a different hand stereotypy (within seconds) e.g., mouth/tap, clasp/clap
Mixed asymmetric hand movements	Any instance in which the hands are midline with a repetitive, nonpurposeful movement, but one hand is less active with the wrist flexed or extended and/or fingers flexed
Repetitive finger movements	Any instance in which there is a pianolike movement of fingers
Other	Any other hand stereotypy that does not fit the above categories (includes arm extension, posturing)