ELSEVIER

Brain & Development xxx (2018) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

The course of awake breathing disturbances across the lifespan in Rett syndrome

Daniel C. Tarquinio [a,b,*], Wei Hou [c], Jeffrey L. Neul [d], Gamze Kilic Berkmen [a,b], Jana Drummond [a,b], Elizabeth Aronoff [a,b], Jennifer Harris [b], Jane B. Lane [e], Walter E. Kaufmann [f], Kathleen J. Motil [g], Daniel G. Glaze [g], Steven A. Skinner [f], Alan K. Percy [e]

[a] *Emory University, Atlanta, GA, United States*
[b] *Center for Rare Neurological Diseases, Norcross, GA, United States*
[c] *Statistical Analysis, Stony Brook University Medical Center, Stony Brook, NY, United States*
[d] *Vanderbilt University, Nashville, TN, United States*
[e] *University of Alabama at Birmingham, AL, United States*
[f] *Greenwood Genetic Center, Greenwood, SC, United States*
[g] *Baylor College of Medicine, Houston, TX, United States*

Received 12 October 2017; received in revised form 15 February 2018; accepted 27 March 2018

Abstract

Rett syndrome (RTT), an X-linked dominant neurodevelopmental disorder caused by mutations in *MECP2*, is associated with a peculiar breathing disturbance exclusively during wakefulness that is distressing, and can even prompt emergency resuscitation. Through the RTT Natural History Study, we characterized cross sectional and longitudinal characteristics of awake breathing abnormalities in RTT and identified associated clinical features. Participants were recruited from 2006 to 2015, and cumulative lifetime prevalence of breathing dysfunction was determined using the Kaplan-Meier estimator. Risk factors were assessed using logistic regression. Of 1205 participants, 1185 had sufficient data for analysis, including 922 females with classic RTT, 778 of whom were followed longitudinally for up to 9.0 years, for a total of 3944 person-years. Participants with classic or atypical severe RTT were more likely to have breathing dysfunction (nearly 100% over the lifespan) compared to those with atypical mild RTT (60–70%). Remission was common, lasting 1 year on average, with 15% ending the study in terminal remission. Factors associated with higher odds of severe breathing dysfunction included poor gross and fine motor function, frequency of stereotypical hand movements, seizure frequency, prolonged corrected QT interval on EKG, and two quality of life metrics: caregiver concern about physical health and contracting illness. Factors associated with lower prevalence of severe breathing dysfunction included higher body mass index and head circumference Z-scores, advanced age, and severe scoliosis or contractures. Awake breathing dysfunction is common in RTT, more so than seizures, and is associated with function, quality of life and risk for cardiac dysrhythmia.

Keywords: Rett syndrome; *MECP2*; Periodic breathing; Dysautonomia; Natural History Study

Abbreviations: *CDKL5*, human cyclin-dependent kinase-like 5 gene; MeCP2, human methyl-CpG-binding protein 2; *MECP2*, human methyl-CpG-binding protein 2 gene; *Mecp2*, murine methyl-CpG-binding protein 2 gene

* Corresponding author at: 5600 Oakbrook Parkway, Suite 120, Norcross, GA 30093, United States.
E-mail address: daniel@rareneuro.com (D.C. Tarquinio).

https://doi.org/10.1016/j.braindev.2018.03.010
0387-7604/

1. Introduction

Rett syndrome is a debilitating neurodevelopmental disorder caused by mutations in *MECP2* and characterized by a constellation of neurological and systemic symptoms that can present as early as the first year of life [1–5]. Individuals with Rett syndrome undergo developmental regression and lose expressive language and hand then cycle through periods of worsening and improvement, most of which are associated with waxing and waning comorbidities such as gastrointestinal dysfunction, seizures, and awake breathing dysfunction [6–8]. Among the varied clinical manifestations associated with Rett syndrome, awake breathing disturbances are troublesome for caregivers to tolerate and complex for clinicians to characterize and manage. Breathing abnormalities in Rett syndrome were noted in passing by Andreas Rett [9], and Hagberg et al., found "episodic hyperpnea" in 66% [10]. After 1983, Rett syndrome was widely recognized, and Lugaresi et al., described polygraphic findings in 4 girls with alternating hyperpnea and apneic episodes associated with cyanosis and syncope, exacerbated by stress during wakefulness and resolving during sleep [11]. They postulated that this phenomenon was the opposite of that in congenital hypoventilation syndrome, and sharply contrasted from self-induced syncopal behavior resulting from the Valsalva maneuver in children with other developmental disorders.

Aside from these cross-sectional observations, the natural history of the awake breathing dysfunction in Rett syndrome remains poorly characterized. Notably, cardiorespiratory dysfunction may account for 26–47% of sudden, unexpected Rett syndrome-associated deaths [12–15]. As many as 14 types of breathing abnormalities have been identified in Rett syndrome that can generally be categorized into two groups: hyperventilation (shallow, fast, and/or forceful breathing), and breath-holding (apnea, Valsalva and/or apneustic breathing) [16–22]. Breathing abnormalities can be further categorized through polygraphy; however, several types of dysrhythmia can present in the same individual, adding to the challenge of classifying the condition [20]. Further, although nearly all reports describe breathing abnormalities in Rett syndrome patients as disappearing during sleep, some describe these during both wakefulness and sleep [7,11,16,23–25]. Although caregivers often report that breathing dysfunction worsens or improves spontaneously, the longitudinal course of breathing dysfunction and the risk factors associated with these fluctuations remain unknown.

Specific categorization of breathing dysfunction is rarely pursued in North American Rett syndrome clinics [26]. Currently no evidence-based treatments for breathing disturbances in Rett syndrome exist; however, improved breathing patterns with specific treatments suggested by several case reports may justify such detailed categorization [27–30]. Moreover, several clinical trials have used outcome measures such as the apnea index, oxygen saturation, and percentage of time with disorganized breathing to document change in respiratory function [31,32].

To understand cross-sectional and longitudinal characteristics of awake breathing abnormalities in Rett syndrome, we analyzed patient data on age of onset, evolution, duration, and severity of breathing disturbances in Rett syndrome obtained from the Rett Syndrome Natural History Study. Because the patterns of hyperventilation and breath-holding cease during sleep, "breathing abnormalities" hereafter refers to "awake breathing abnormalities". We also elucidated associations between breathing disturbances and Rett syndrome-associated clinical features, *MECP2* mutations, diagnosis, mortality, and quality of life to gain insights into predictors and consequences of breathing disturbances.

2. Materials and methods

2.1. Participants

Participants were recruited, as described previously [33,34], from 2006 to 2015 through the multicenter Rett Syndrome Natural History Study at one of eight US sites and evaluated every 6–12 months. The Rett Syndrome Natural History Study consortium is part of the Rare Diseases Clinical Research Network, an initiative of the Office of Rare Diseases Research, National Center for Advancing Translational Sciences. Diagnosis of Rett syndrome phenotype and epilepsy was performed by a study neurologist or geneticist (DGG, WEK, JLN, AKP, and SAS) with extensive clinical experience in Rett syndrome. Consensus criteria [35,36] were used to categorize participants as having classic Rett syndrome, atypical Rett syndrome, or a mutation in *MECP2* but not fulfilling clinical criteria for Rett syndrome (hereafter *MECP2* mutation without Rett syndrome). All participants had *MECP2 testing*; participants with clinical Rett syndrome were included even if they lacked a mutation. Further details have been published previously, including age of symptom onset and diagnosis, and age and cause of death [12,33,34,37]. History of onset and frequency of awake breathing dysfunction and associated comorbidities was recorded at the first encounter and updated at each subsequent visit. Breathing during sleep is not discussed in this manuscript. Demographic data included race and ethnicity, type of residence, and parental age. Socioeconomic data (median income and population density) were estimated using US census data based on postal

Please cite this article in press as: Tarquinio DC et al. The course of awake breathing disturbances across the lifespan in Rett syndrome. Brain Dev (2018), https://doi.org/10.1016/j.braindev.2018.03.010