Multisystem comorbidities in classic Rett syndrome: a scoping review

Cary Fu,1 Dallas Armstrong,2,3 Eric Marsh,2,3 David Lieberman,4 Kathleen Motil,5,6 Rochelle Witt,4 Shannon Standridge,7,8 Jane Lane,9,10 Tristen Dinkel,11 Mary Jones,12 Katie Hale,12 Bernhard Suter,13,14 Daniel Glaze,13,14 Jeffrey Neul,15,16 Alan Percy,17 Timothy Benke11,18

ABSTRACT

Background Rett syndrome (RTT) is a severe, progressive neurodevelopmental disorder with multisystem comorbidities that evolve across a patient’s lifespan requiring attentive coordination of subspecialty care by primary care providers. A comprehensive, up-to-date synthesis of medical comorbidities in RTT would aid care coordination and anticipatory guidance efforts by healthcare providers. Our objective was to review and summarise published evidence regarding prevalence of RTT medical comorbidities across all relevant organ systems.

Methods Search of PubMed from January 2000 to July 2019 was performed using the search terms (Rett and MECP2 AND patient) OR (Rett and MECP2 AND cohort). Articles reporting the prevalence of clinical findings in RTT were assessed with respect to the size and nature of the cohorts interrogated and their relevance to clinical care.

Results After review of over 800 records, the multisystem comorbidities of RTT were summarised quantitatively from 18 records comprising both retrospective and prospective cohorts (31–983 subjects). Neurological comorbidities had the highest prevalence, occurring in nearly all individuals with gastrointestinal and orthopaedic issues. Endocrine and cardiac abnormalities were seen in only around one-third of patients. Although more prevalent compared with the general population, cardiac conduction abnormalities were the least common comorbidity in RTT.

Conclusions Effective care coordination for RTT requires knowledge of and attention to multiple comorbidities across multiple unrelated organ systems. Many issues common to RTT can potentially be managed by a primary care provider but the need for sub-specialist referral can be anticipated. Since the median life expectancy extends into the sixth decade with evolving subspecialty requirements throughout this time, paediatric providers may be tasked with continued coordination of these comorbidities or transitioning to adult medicine and specialists with experience managing individuals with complex medical needs.

INTRODUCTION

Classic (typical) Rett syndrome (RTT)1 is a severe, progressive neurodevelopmental disorder occurring in approximately 1 in 10 000 female births.2 There is an estimated worldwide prevalence of between 1 in 20 000 and 40 000 people making2 it one of the most common genetic causes of developmental and intellectual impairment in females.3 The syndrome is characterised by an initial period of normal development followed by psychomotor regression, deceleration of head growth and development of distinctive repetitive, purposeless hand movements.4,5 Due to symptom evolution over time, RTT is considered a progressive disorder but, contrary to a long-held misconception, it is not a neurodegenerative condition.7 RTT is caused by >300 distinct loss-of-function mutations in the gene MECP2 (methyl-CpG binding protein-2) on the X-chromosome.8 The MECP2 protein is an essential transcriptional regulator in the brain required for normal neurodevelopment.9 Due to major strides in understanding the molecular pathogenesis over the past three decades and successful reversal
of symptoms in mouse models, there is optimism for disease modifying therapies in the future.

Despite the present inability to modify the course of the disorder at a mechanistic level, over two decades of research on the natural history of RTT has shown us that with appropriate symptom-directed care, people with RTT can live long and meaningful lives. Compared with an estimate of survival using historical data from the earliest published cohort of people with RTT which found very low rates of survival beyond the third decade of life, analyses of modern cohorts demonstrate markedly improved survival as symptom management has evolved with the most recent report from a large North American longitudinal cohort finding 70% of individuals with typical RTT surviving to at least 50 years of age. The multisystem involvement of the disorder with comorbidities that evolve throughout a patient’s lifespan thus present a significant challenge to the physicians tasked with effectively coordinating the management of these symptoms which will often require subspecialty consultation.

While there have been many publications over the past 20 years addressing individual organ system comorbidities in RTT, a comprehensive synthesis in accordance with the multisystem involvement of the disorder would provide a global understanding of RTT and better facilitate the daunting challenge of effective care coordination. To address this challenge, we performed a review of published literature regarding RTT symptomatology with the goal of delineating the prevalence of comorbidities across all organ systems.

METHODS

Database search

In July 2019 we performed a search of PubMed (from 2000) using the search terms (Rett and MECP2 AND patient) OR (Rett and MECP2 AND cohort). Due to the anticipated low number of articles addressing symptom prevalence, we implemented a broad initial search strategy to minimise the likelihood of excluding relevant articles. Full details of the literature search strategy are described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram presented in figure 1.

Article selection

We defined the inclusion and exclusion criteria for final article selection with input from patient advocacy group representatives. From the initial search criteria we first excluded articles that were not in English (n=40), did not have full-text access (n=9), focused solely on non-clinical topics (n=493) or were related to disorders other than RTT (n=145). Next, from the resulting full-text articles (n=157) we included only articles reporting on classic RTT containing data relevant to clinical care (n=104). We worked as a group to select articles based on the inclusion criteria with the group leader (TAB) moderating the process. The selection process comprised two stages: an initial stage involving title and abstract review and second stage involving the full-text. All authors participated at both stages. We used the final list of 104 articles for a qualitative synthesis informing general clinical guidance (‘Consensus guidelines on managing Rett Syndrome across the lifespan’ (Fu C, et al. BMJ Paediatrics Open 2020, in press)). For the final quantitative synthesis we only included articles (n=18) specifically describing prevalence of clinically relevant comorbidities in cohorts of ≥30 subjects that had not been superseded by a more recent publication studying the same comorbidity in a larger (at least one order of magnitude) cohort (‘outdated’).

Patient advocacy group involvement

Patient advocacy groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT, provided feedback on the relevance of the literature review. They will help disseminate these findings as part of ‘Consensus guidelines on managing Rett Syndrome across the lifespan’ (manuscript accepted for publication).

RESULTS

Our search strategy (figure 1) yielded 844 citations that were screened further by title and abstract. Of these, 687 articles were excluded, leaving 157 full-text articles for more detailed review. From the detailed review 104 articles were retained for a qualitative synthesis of clinical care guidelines in RTT (manuscript in preparation). These articles originated from countries throughout the world including USA, Australia, Canada, UK, Italy, Austria, The Netherlands, Sweden, Turkey, Portugal and Israel. Most (79%) of the articles involved original research studies or review articles that did not specifically address prevalence of non-neurological comorbidity but were informative for clinical management and there were a small number (5%) of articles that reported prevalence data from small prospective cohorts. Importantly, 18 articles (17%) specifically quantified the prevalence of clinically relevant comorbidities in large cohorts of patients with classic RTT. These articles were then used for the quantitative synthesis regarding prevalence of medical comorbidities (table 1).

The characteristics of the 18 included studies are presented in table 2. Most of the articles were from North America: 11 articles from the USA and 1 from Canada; additionally, there were 4 articles from Australia, 1 from Portugal and 1 from Italy. The cohort size ranged from 31 to 983 subjects. The study designs were divided equally between prospective (9 of 18 articles) and cross-sectional assessments (9 of 18 articles). Most of the prospective studies (8 articles) involved in person assessments; 5 studies with multisite data collection and 3 studies with single institution cohorts. A single prospective study used a national patient registry capturing data.
The multisystem nature of the disorder is quite apparent based on the observational studies identified in this scoping review (table 2). As expected for a neurodevelopmental disorder, neurological concerns are the most prevalent of all comorbidities (table 1) including autonomic dysregulation, epilepsy, swallowing dysfunction, sleep dysfunction, abnormal movements and behaviour disturbances. The autonomic dysregulation manifests most prominently as an irregular breathing pattern which occurs in nearly 100% of individuals with RTT over the lifespan with the majority presenting by age four with varying levels of rapid breathing, breath-holding and/or air-swallowing that fluctuate in intensity while awake and disappear during sleep. Epilepsy is nearly as prevalent as breathing irregularity with nearly 90% of individuals receiving this diagnosis across the lifespan, the majority by 6 years of age. Impaired swallowing function has equal prevalence to epilepsy over the lifespan but becomes apparent at a younger age often manifesting in early childhood as prolonged feeding times, choking/gagging on food and/or aspiration of liquids. Sleep dysfunction was another highly prevalent neurological comorbidity reported in around 90% of individuals manifesting as difficulty falling asleep and/or staying asleep with important impacts on overall family quality of life. Behaviour disturbances occur in nearly all individuals with RTT across the lifespan with internalising behaviours such as anxiety or mood swings being much more common overall than externalising behaviours such as aggression, hyperactivity or self-injury which are seen in about 40% of individuals, almost always with onset before 3 years of age and which improve over time in contrast to the internalising behaviours. Outside of the repetitive hand movements that are part of the
main diagnostic criteria of typical RTT, additional movement abnormalities are found in 60%–80% involving varying combinations of dystonia, tremor, myoclonus, chorea and progressive limb rigidity with bradykinesia resembling parkinsonism.20–22

In addition to the highly prevalent neurodevelopmental issues, gastrointestinal and orthopaedic comorbidities are also quite prevalent, each reported in over 80% of individuals. 29 30  The gastrointestinal issues resembling parkinsonism.20–22 chorea and progressive limb rigidity with bradykinesia varying combinations of dystonia, tremor, myoclonus, mental abnormalities are found in 60%–80% involving main diagnostic criteria of typical RTT, additional movement abnormalities causing impaired gastrointestinal motility. Poor growth is reported in around 40% of individuals

primarily involving impaired weight gain and/or linear growth deficits.29 The impaired growth is thought mostly secondary to chewing/swallowing dysfunction causing inadequate caloric intake because improvements in height and weight gain are seen after calorie supplementation via gastrostomy tube.33 Biliary tract disease does not appear to impact individuals with RTT at a higher rate (4%) than the general population but may be difficult to recognise due to non-specific symptoms overlapping with behaviour disturbances and the underlying communication impairments in RTT.30 Scoliosis is the most frequently encountered orthopaedic issue with 85% of individuals 16 years or older diagnosed with this finding. Its occurrence is age-dependent though with much lower prevalence in childhood and increasing prevalence through adolescence.19 Additional important orthopaedic complications include hip displacement (either subluxation or dislocation) that may be seen in a little over half of individuals32 and also a three to four fold higher prevalence of bone fractures compared with typically developing individuals.24 28 The high prevalence of fractures is potentially linked to low bone mineral content in RTT which is the most common endocrine comorbidity that is seen in over half of individuals beginning in childhood.28 The timing of secondary sexual characteristics is also frequently altered in RTT with early adrenarche or thelarche in a quarter and just under 20% with delayed menarche.18 Above normal levels of thyroid hormone are also found in about 20% but the clinical implications of this are unclear.27 Finally, cardiac conduction abnormalities involving prolonged QT interval are seen in 10%–18%.25 26

DISCUSSION
Based on our approach with the literature to date, the comprehensive list of clinically relevant comorbidities in RTT is considered to be complete, especially due to the experiences with larger cohorts. There are some limitations with our approach to estimate the prevalence of these comorbidities. While we have selected articles whenever possible based on the best available evidence (level 3) involving medium to large cohorts with prospective data collection, there is the potential for bias because many of the studies analysed were generated from the authors’ own experience and approach with the largest cohort via the National Institutes of Health-funded Natural History Study of Rett and related disorders (National Health Service, U54 HD061222; ClinicalTrials.gov: NCT00299312/NCT02738281). This study required in-person assessments for data collection and as such potentially subject to ascertainment bias, however, generalisability is supported by similar prevalence findings when the same comorbidity was reported in different and unique cohorts with population-based sampling.5 13 The approach included studies with at least 30 subjects whenever larger cohorts were not available for a comorbidity. These smaller studies may miss the true prevalence

| RTT comorbidities                  | Prevalence (%) | Studies                          |
|-----------------------------------|----------------|---------------------------------|
| Neurological                      |                |                                 |
| Irregular breathing pattern       | 95             | Tarquinio et al16               |
| Epilepsy                          | 90             | Tarquinio et al17               |
| Dysphagia                         | 90             | Motil et al23                   |
| Sleep dysfunction                 | 93             | Boban et al31                   |
|                                   | 80             | Wong et al25                    |
| Movement disorders                | 84             | Humphreys et al26              |
|                                   | 63             | Temudo et al21                 |
|                                   | 63             | FitzGerald et al22              |
| Behavioural disturbance, any      | 97             | Buchanan et al15                |
| Behavioural disturbance (on med)   | 14             |                                 |
| Gastrointestinal/nutrition        |                |                                 |
| Constipation                      | 80             | Motil et al23                   |
| Reflux                            | 40             | Motil et al23                   |
| Growth abnormalities              | 40             | Motil et al23                   |
| Underweight                       | 38             |                                 |
| Short stature                     | 45             |                                 |
| Gall bladder dysfunction          | 4              | Motil et al23                   |
| Cardiac                           |                |                                 |
| Prolonged QT interval             | 18             | McCauley, et al25              |
|                                   | 10             | Crosson et al28                 |
| Endocrine                         |                |                                 |
| Low bone mineral mass             | 59             | Motil et al23                   |
| Premature adrenarche              | 28             | Killian et al18                 |
| Premature thelarche               | 25             | Killian et al18                 |
| Delayed menarche                  | 19             | Killian et al18                 |
| Thyroid dysfunction               | 18             | Stagi et al67                   |
| Orthopaedic                       |                |                                 |
| Scoliosis                         | 80             | Percy et al18                   |
| Hip displacement                  | 50             | Tay et al12                     |
| Fractures                         | 32             | Jefferson et al24               |
|                                   | 28             | Motil et al23                   |

RTT, Rett syndrome.
of specific RTT comorbidities. Recruiting large cohorts is always a challenge in rare disease research and the recruitment of subjects with extreme symptoms and medically fragile conditions may be more difficult outside of a clinical setting. The smallest cohorts included in this synthesis were ascertained from clinical settings. These cohorts, though smaller, may reflect a fuller spectrum of disease severity.

While it is possible that some of the prevalence estimates of medically relevant RTT comorbidities require further investigation to be reliably generalisable, the available information supports the medically complex nature of this disorder and the importance of coordinating care across multiple specialties. Until additional features are better resolved through longer observations in large cohorts, especially in those that include the older and most medically fragile individuals with RTT, medical features outside this list must be considered to not be comorbid with RTT and are deserving of further medical investigations to determine their aetiology.

In conclusion, RTT is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the sixth decade of adulthood. With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living healthier and more meaningful lives. Primary care providers are uniquely positioned to most effectively manage the individual and family by drawing on the accumulating knowledge regarding the natural history of the disorder to anticipate and coordinate the complex multidisciplinary requirements. When children with RTT grow into adulthood, paediatricians may be tasked with continued care coordination for these comorbidities or transitioning primary care to adult medicine specialists with experience managing individuals with complex medical needs.

**Table 2** Description of articles included in the quantitative synthesis of Rett syndrome comorbidities

| Study design | Author          | Country          | Cohort size (n) | Age range (years) |
|--------------|-----------------|------------------|-----------------|-------------------|
| Prospective cohort | Buchanan et al<sup>15</sup> | USA              | 861             | 3–66              |
|               | Tarquinio et al<sup>16</sup> | USA              | 778             | 0.7–66.5          |
|               | Tarquinio et al<sup>17</sup> | USA              | 922             | 0.7–66.5          |
|               | Humphreys et al<sup>20</sup> | Canada           | 51              | 2.5–54            |
|               | Wong et al<sup>23</sup>     | Australia        | 320             | 2–35.8            |
|               | Killian et al<sup>18</sup>  | USA              | 802             | 3–70              |
|               | Percy et al<sup>19</sup>    | USA              | 554             | 0–57              |
|               | Temudo et al<sup>21</sup>  | Portugal         | 60              | 5–13.5            |
|               | FitzGerald et al<sup>22</sup> | USA              | 32              | 2.5–28            |
| Cross-sectional | Motil et al<sup>20</sup>  | USA              | 271             | 7, 19*            |
|               | Boban et al<sup>31</sup>   | Australia        | 364             | 2–57              |
|               | Crosson et al<sup>26</sup> | USA              | 100             | 1–17              |
|               | Stagi et al<sup>27</sup>   | Italy            | 45              | 2–26.1            |
|               | Motil et al<sup>29</sup>   | USA              | 983             | 0–40+             |
|               | Jefferson et al<sup>24</sup> | Australia     | 97              | 4–30.5            |
|               | McCauley, et al<sup>25</sup> | USA              | 379             | 2–46              |
|               | Tay et al<sup>32</sup>     | Australia        | 31              | 7–29              |
|               | Motil et al<sup>28</sup>   | USA              | 50              | 2–38              |

*Reported as first, third quartile.
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ORCID iD  Timothy Benke http://orcid.org/0000-0002-6969-5061

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