Review article

Organic features of autonomic dysregulation in paediatric brain injury – Clinical and research implications for the management of patients with Rett syndrome

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ABSTRACT

Rett Syndrome (RTT) is a complex neurodevelopmental disorder with autonomic nervous system dysfunction. The understanding of this autonomic dysregulation remains incomplete and treatment recommendations are lacking. By searching literature regarding childhood brain injury, we wanted to see whether understanding autonomic dysregulation following childhood brain injury as a prototype can help us better understand the autonomic dysregulation in RTT. Thirty-one (31) articles were identified and following thematic analysis the three main themes that emerged were (A) Recognition of Autonomic Dysregulation, (B) Possible Mechanisms & Assessment of Autonomic Dysregulation and (C) Treatment of Autonomic Dysregulation. We conclude that in patients with RTT (I) anatomically, thalamic and hypothalamic function should be explored, (II) sensory issues and medication induced side effects that can worsen autonomic function should be considered, and (III) diaphoresis and dystonia ought to be better managed. Our synthesis of data from autonomic dysregulation in paediatric brain injury has led to increased knowledge and a better understanding of its underpinnings, leading to the development of application protocols in children with RTT.

1. Introduction

Rett Syndrome (RTT) is a neurological disorder starting in early childhood caused in most cases by mutations in the epigenetic modulator methyl-CpG binding protein 2 (MECP2) (Iatza et al., 2017). One key feature of RTT is the presence of Emotional, Behavioural and Autonomic Dysregulation (EBAD). EBAD is often a neglected issue, and a lack of understanding of it hinders more effective treatment plans and clinical management. It presents with a constellation of symptoms, and the autonomic component is pivotal for driving the behavioural and emotional symptoms observed in this patient group (Singh and Santosh, 2018). This finding is important because a dysregulated sympathovagal balance can reduce the vagal tone in neurodevelopmental disorders (Engineer et al., 2017). Reduced vagal activity is linked to both behavioural and emotional impairments (Cheshire, 2012) and the impaired sympathovagal balance caused by the underlying autonomic dysfunction itself in RTT can frequently be the cause of treatment non-response or atypical responses to treatment. The pervasive nature of the autonomic dysregulation seen in patients with RTT suggests, however, that there is unlikely to be a unifying mechanism that can explain the different symptoms seen in EBAD across patient groups. Our working model has recently suggested that in RTT, the disordered neurotrophic maturation of brainstem networks increases the vulnerability of this population to autonomic crisis leading to catastrophic changes in cardio-respiratory homeostasis (Singh et al., 2020). We reasoned that the failure to prune neural networks in this patient group extending...
beyond the foetal epoch causes the aberrant cardio-respiratory dysfunction as the disorder advances.

While there is no clear consensus on the age of diagnosis of RTT, the median age at diagnosis of 1085 participants from the RTT Natural History Survey was 2.7 years (Tarquinio et al., 2015). Before this period, there is a period of developmental regression that usually appears between 12–19 months and is accompanied by both behavioural and emotional delay (Einspieler and Marschik, 2019). At birth, the defects underpinning autonomic dysfunction in Rett patients have already been consolidated. However, from an autonomic perspective, this points towards an epoch of autonomic quiescence before the core development impairments emerge. This premise is supported by the observation that autonomic dysregulation and its associated symptoms do not occur at birth. Indeed, by 5 years of age, respiratory dysrhythmias such as breath holding, and hyperventilation appear in about 60 % and 50 % of Rett children, respectively (Mackay et al., 2017). Rett animal models further indicate that breathing dysregulation manifests after seemingly normal post-natal development (Katz et al., 2009). Also, abnormalities in cardiac repolarisation such as changes in T waves appear to occur more frequently in Stages III and IV in comparison to Stage I (Sekul et al., 1994). These observations underscore the unique development plasticity of the autonomic nervous system (ANS) driving these changes in RTT. It shows that across the patient group even though the autonomic dysregulation is disrupted well before birth, the symptoms of autonomic dysregulation can appear at different neurodevelopmental milestones.

Yet during this period of autonomic quiescence, plasticity is seemingly stable enough that no apparent symptoms of EBAD emerge in Rett patients. Based on previous literature evidence and clinical experience of observing Rett patients in the Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), we have proposed that autonomic dysfunction follows a non-linear trajectory in Rett patients (Singh et al., 2020) and given the divergent autonomic profile seen in patients (Pini et al., 2016) it can ‘re-emerge’ or ‘catch-up’ as the disorder advances. Despite this proposal, we are mindful that this hypothesis has not yet been proven clinically and further work would be needed to test it in other external clinical settings. The clinical symptoms of EBAD can be sporadic and from a behavioural viewpoint, some evidence has also shown that the emergence of behavioural regression can be quite sudden (Witt-Egerström, 1987).

While our previous work has illuminated some themes relating to the mechanism of autonomic dysregulation in Rett patients, as far as we are aware the organic features of several aspects of autonomic dysregulation in these patients remains incomplete. We know that the autonomic dysregulation in Rett compares to that of preterm infants (Singh et al., 2020). Still, gaps remain when it comes to an understanding of the clinical signs and potential triggers for the dysregulation in the younger age group. These gaps highlight the problems in managing autonomic dysregulation in the clinical setting, especially in children with RTT. This raises the question of whether it would be possible to address the gaps in knowledge of autonomic dysregulation in Rett patients from studies of brain injury in children where autonomic dysregulation is a common clinical finding. The overall goal of this study was, therefore, to investigate whether the key findings from studies in children with autonomic dysregulation following brain injuries can be extrapolated to further our understanding of the autonomic dysregulation seen in children with RTT.

Autonomic dysregulation is a serious pathogenic sequela of childhood brain injury (ABI). In children, the degree of the autonomic dysregulation varies according to the type of brain injury. It ranges from 12 % to 29 % in children with traumatic brain injury (TBI) or hypoxic brain injury respectively (Kirk et al., 2012). A characteristic feature of post-TBI is an impairment of the cardiac autonomic control system (Gregory and Smith, 2012). Autonomic dysregulation arising from a brain injury can manifest itself as distinct changes in heart rate variability parameters. For TBI, it has been suggested that a desynchronisation of the para-sympathetic and sympathetic arms of the ANS caused by cortical and/or hypothalamus dysregulation (Baguley et al., 2008) may be the underlying cause alongside sympathetic storming (Lemke, 2007). These features of autonomic dysregulation originating from childhood brain injury are suggested to mirror those observed in RTT because in both instances the resulting autonomic imbalances cause a cardiovascular dysregulation that is reflected by changes in cardiac physiology. In addition, troponin, an insulin like growth factor analogue is being evaluated in Rett patients (Glaze et al., 2019, 2017) and in those with traumatic brain injury (https://clinicaltrials.gov/ct2/show/NCT00805818). The rationale is based on the evidence that both RTT and TBI share common pathological pathways such as disordered microglial activation (Karve et al., 2016; Derecki et al., 2013). These observations show that (I) brain injury and RTT might share common features regarding autonomic dysfunction and (II) studies evaluating heart rate metrics of autonomic dysfunction in children with brain injury are useful for the purposes of identifying possible biomarkers of EBAD in RTT. We hypothesise that exploring the underlying mechanisms of autonomic dysregulation caused by brain injury in children following acute ABI (such as that caused by injury, i.e. TBI) and comparing it to the dysregulation seen in Rett patients would provide valuable insights into the mechanism and clinical trajectory of EBAD especially when it comes to defining reliable treatment strategies.

1.1. Aim and Objectives of this review

As far as we are aware, no studies have searched for autonomic dysregulation arising from a brain injury in children to inform the autonomic correlates seen in Rett patients. By using an empirical framework of studies done in children with brain injury, the aim of this systematic review was to evaluate and assess research studies regarding autonomic dysregulation in children with brain injury with a view to identify comparable neurophysiological correlates of autonomic dysregulation that can be used to assist in the management of EBAD in Rett patients.

Given the complex symptom profile of children with RTT, further understanding of the mechanism of autonomic dysregulation would be a critical step for assisting in early diagnosis and referral for children with RTT. The objectives of this review were, therefore (I) to identify the organic features of autonomic dysregulation in children with brain injury (II) to identify emerging themes and extrapolate the key findings to Rett patients and (III) to provide application protocols for the management of autonomic dysregulation in these patients to understand its impact on neurodevelopmental milestones.

2. Methods

2.1. Search strategy

Following published PRISMA guidelines (Liberati et al., 2009), to capture the relevant literature on autonomic dysfunction in children with brain injury, the electronic search of the databases was performed blindly and independently by the authors JS and EL in December 2019. For this purpose, the search terms and words that were used were:

(Acquired Brain Injury OR Traumatic Brain Injury OR Brain Injury OR autonomic storm*) AND (Autonomic Dysfunction OR Autonomic Dysregulation) AND (child OR children OR infant)

The databases that were searched were Pubmed, Scopus, Cochrane, PsycINFO, Embase and Web of Science databases. No year restrictions were applied. Boolean operators ‘AND’ ‘OR’ were used to link the search terms and truncation symbols (*) were used to make the search strategy as comprehensive and focused as possible.

2.1.1. Population characteristics

Studies were used in which children had a brain injury and autonomic impairment.
2.1.2. Intervention
All studies that reported autonomic dysregulation/dysfunction were included.

2.1.3. Eligibility criteria
The following inclusion and exclusion criteria were used:

Inclusion Criteria
- English language articles in peer-reviewed academic/scientific journals.
- Full-text articles available electronically.

Exclusion Criteria
- Studies done in animal models.
- Book chapters, review articles, conference abstracts, articles in press and single case reports.

2.2. Qualitative data analysis
The data was extracted from the eligible articles and information relating to the core findings from the articles were analysed. The thematic analysis was undertaken as previously described (Singh et al., 2020). We are aware that a truly inductive analysis of themes would not be possible due to our previous understanding in the subject area. Nevertheless, as far as it was possible, the qualitative analysis was data-driven without theoretical interest. Coding was first done manually by JS, who examined the eligible articles to establish preliminary themes from the extracted data. These preliminary themes were then reviewed independently by EL. Following this review, alignment was reached by JS and EL, and the final themes that emerged were established following consensus agreement between all the authors. Microsoft Excel 2016 was used to present the frequency of each theme.

3. Results
3.1. Identification of Eligible Articles
After screening, the PRISMA flow-chart (Fig. 1) revealed 571 records, of which 517 were excluded. Fifty-four (54) full-text articles were screened against the eligibility criteria, and 23 were excluded. The remaining 31 were included for the qualitative thematic analysis.

Fig. 1. PRISMA flow-chart of systematic review.
3.2. Thematic Analysis

Commentary and relevant information from the 31 analysed articles are presented in Table 1. From the thematic analysis of the findings related to autonomic dysfunction within the 31 articles, five themes emerged. The frequency of the themes is shown in Fig. 2A and listed below:

Theme 1: Impaired Autonomic Metrics following Brain Injury
Theme 2: Clinical Signs and Possible Risk Factors for Autonomic Dysregulation
Theme 3: Pharmacological Management of Autonomic Dysregulation
Theme 4: Anatomical Localization of Brain Damage
Theme 5: Disruption of Catecholamine Levels and Pro-Inflammatory Cytokine Release

The theme ‘impaired autonomic metrics following brain injury’ emerged from eight studies (Sorek et al., 2018; Campbell et al., 2018; Metzler et al., 2017; Kim et al., 2017; Vergales et al., 2014; Katz-Leurer et al., 2010; Biwas et al., 2006; Goldstein et al., 1996). Themes emerging from ‘clinical signs and possible risk factors for autonomic dysregulation’ and ‘pharmacological management of autonomic dysregulation’ emerged from eight studies respectively (Pozi et al., 2019; Reich et al., 2019; Pucks-Faes et al., 2018; Letzkus et al., 2018a, b; Pozi et al., 2017; Farias-Moeller et al., 2015; Deepika et al., 2015; Kirk et al., 2012; Hoarau et al., 2012a, b; Lv et al., 2011; Chelly et al., 2011; Baguley et al., 2007, 2004; Meythaler and Stinson, 1994). The theme related to ‘anatomical localization of brain damage’ emerged from six studies (Reich et al., 2019; Mrkobrada et al., 2016; Thiriez et al., 2015; Menteer et al., 2016; Lv et al., 2010; Krach et al., 1997) and the theme with the lowest frequency was ‘disruption of catecholamine levels and pro-inflammatory cytokine release’ that emerged from two studies (Al-Shargabi et al., 2017; Goldstein et al., 1996). Following an agreement between all the authors, these five themes were grouped into three final themes (Fig. 2B and C):

Theme A: Recognition of Autonomic Dysregulation
Theme B: Possible Mechanisms & Assessment of Autonomic Dysregulation
Theme C: Treatment of Autonomic Dysregulation

These themes will be discussed in the next section:

3.3. Theme A: Recognition of Autonomic Dysregulation

The evidence that best supported this theme emerged from those studies that examined clinical signs of autonomic dysregulation following paediatric brain injury. Autonomic dysregulation, venous, respiratory and feeding devices appeared to have the most significant relationship to ‘anatomical localization of brain damage’ following paediatric brain injury. Autonomic dysregulation, venous, respiratory and feeding devices appeared to have the most significant relationship to ‘anatomical localization of brain damage’ following paediatric brain injury.

3.4. Theme B: Possible Mechanisms & Assessment of Autonomic Dysregulation

3.4.1. Possible mechanisms of autonomic dysregulation

When analysing the eligible articles, damage to the thalamus can be considered as a predictor for the severity and length of autonomic dysregulation following hypoxic brain injury (Mrkobrada et al., 2016). Neuronal function within the thalamus of Rett patients is underexplored. Some studies have highlighted that there is impaired GABAergic circuit functioning within the thalamus of animal models of Rett (Zhang et al., 2010) and that mirtazapine can ameliorate some of the associated circuit dysfunction (Bittolo et al., 2016). Given the small sample sizes of studies done in paediatric brain injury, whether these findings would also be applicable to the Rett population remains unknown at present. However, it might be useful to explore brain functioning in the Rett patient group using functional near-infrared spectroscopy (fNIRS) to provide further insight into the autonomic dysregulation. In patients with Rett, conventional neuroimaging approaches are not readily suited because sedation is often required. fNIRS is a non-invasive imaging technique for studying functional activations by measuring changes in the hemodynamic properties of the brain and has been used to study brain development in children on the autism spectrum (Liu et al., 2017). It is intolerant of participant motion and could be one option for assessing brain functioning in real time in patients with Rett.

In cases where severe heart failure occurred, decreases in the volume of gray matter might be associated with the autonomic decline (Menteer et al., 2010). When exploring the broader clinical picture using brain imaging, assessment of the longer-term impact of risk factors associated with autonomic dysregulation in patients with severe TBI over a 24-month duration revealed damage to brainstem structures in those with PSH (Lv et al., 2010). This suggests that injury to the brainstem could also be associated with poor functional recovery following TBI. In an earlier study of 31 children with central autonomic dysfunction, enlargement of brain ventricles was noted after brain injury (Krach et al., 1997). In patients with Rett the neuroimaging picture remains incomplete. In a small study consisting of seven females with MECP2 mutations aged 5.2 years at the time of scan, quantitative surface- and voxel-based morphology showed no change in brain ventricles and gray matter volume but reduced cerebellar volumes (Shiohama et al., 2019). An earlier study of 23 Rett girls aged 5–12-year-old revealed decreases in parietal lobe gray matter (Carter et al., 2008) when compared to typically developed individuals. When viewed together, the findings show that the anatomical changes to brain regions following childhood brain injury and those in Rett syndrome vary. The findings in Rett are far from definitive and studies with a larger sample would be needed to identify neuroanatomical changes in patients with autonomic dysregulation. Nevertheless, the different anatomical localizations show that many brain regions are implicated in autonomic dysregulation. This is not surprising because the pervasive nature of the central autonomic network suggests that multiple neuroanatomical areas are likely to be involved.
### Table 1: Summary of Eligible Studies

| Source                    | Study Group                                                                 | Demographics and Clinical Characteristics                                                                 | Assessment Methods                                                                 | Key findings relating to Autonomic Dysfunction                                                                 |
|---------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Pozzi et al. (2019)       | Review of clinical records of patients with sABI injury of traumatic (n=280) and non-traumatic origin (n=292) discharged from ICU into paediatric neurological rehabilitation | Mean age at injury was 6.7 ± 4.7 years<br>Median GCS of 6<br>Duration of rehabilitation was 121.9 ± 72.9 days. | Retrospective clinical record evaluation. The following variables were coded from the clinical records: gender, causation of the severity of ABI (autoimmune encephalitis, brain tumor, hypoxic injury, infective encephalitis, stroke, trauma), sABI date; admittance date and GCS. | Following admittance, autonomic dysregulation was seen in 12.6 % of patients. The greatest contribution to the neurological dysregulation was due to the autonomic dysregulation and the use of venous access, and respiratory and feeding devices. In the study population the incidence of autonomic dysregulation in patients with severe hypoxic ABI was four-fold higher when compared to the other causes of sABI. The autonomic dysregulation can be considered as a proxy measure in terms of the assessing the severity of neurological impairment and its impact on rehabilitation outcomes. As the majority of strokes in newborns are localized to the unilateral middle cerebral artery (MCA) area, the MCA stroke model was used to assess the impact of stroke laterality and severity on autonomic function in newborns. The study findings revealed that stroke in the right versus the left hemisphere was shown to increase sympathetic tone in comparison to left MCA stroke that was linked to an increase in parasympathetic tone. The LF/HF ratio (mean ± SD) was 1.706 ± 0.804. Phenobarbital increased sympathetic but decreased parasympathetic tone. It also has a negative effect on the sympathovagal balance: LF/HF (~–0.003, P=0.037) In contrast to autonomic metrics based on HRV, systemic cardiovascular outputs such as BP and HR showed no change. Neither stroke laterality nor injury to either insular region had an impact on autonomic function. Intrathecal baclofen improved the symptoms of PSH following severe TBI in patients as reflected by stabilisation of HR and BP, and reduction in spasticity. Intrathecal baclofen circumvented the use of oral baclofen treatment that could be stopped after a few days and oral propranolol after a few weeks. Intrathecal baclofen could be considered with other first-line medications for the treatment of autonomic dysregulation flowing severe TBI. Except for spasticity treatment (P=0.048) there were no difference in the Grados scale, etiology of injury, initial GCS score presentation and medical comorbidities between the PSH and non-PSH groups. Significant differences for age (P<0.001), etiology of injury (P=0.03) and those receiving low |
| Reich et al. (2019)        | Sixteen (16) term newborns with unilateral middle cerebral artery strokes (n=8, left and n=8, right) | Gestational age (weeks) (mean ± SD): 39.0 ± 1.2<br>Clinical evidence of seizures was confirmed in all newborns. All newborns received phenobarbital as first line anti-seizure medication. | ECGs were recorded for 24 h from newborns (around their seventh day) who had been seizure free for 48 h but continued to receive phenobarbital. The R-R interval was used to study HRV. Continuous video EEG recordings. Stroke was characterized using MRI and the stroke severity was determined using the modified paediatric ASPECT score. | |
| Pucks-Faes et al. (2018)   | Retrospective assessment of 20 patients with autonomic dysregulation who had been treated with intrathecal baclofen following severe TBI. | Mixed age population with a mean age of 28 ± 11 years (range 8-52 years)<br>Age at accident of four patients (<18 years of age) were 8, 14, 16 and 17 years with a GCS of 8, 3, 3 and 3 respectively. Autonomic dysregulation was characterized in the population as those having PSH | The effect of intrathecal baclofen on PSH was assessed using cardiovascular parameters HR and BP. Rating scales such as the Ashworth Scale for the impact of intrathecal baclofen on spasticity at admission and discharge. | |
| Letzkus et al. (2018a)     | Secondary assessment of a clinical dataset composed of 83 children that had severe ABI to explore the characteristics between the PSH (n=39) and non-PSH (n=44) groups. | PSH group (n=39):<br>Age: 15.13 years ± 7.50;<br>GCS: 3.75 ± 1.0; Grados scale: 4.06 ± 1.85<br>Non-PSH group (n=44):<br>Age: 15.35 years ± 7.69;<br>GCS: 4.24 ± 1.2;<br>Grados scale: 4 ± 1.97 | The Grados scale was used to predict the severity of injury. Rating scales such as the Rancho Los Amigos (RLA) scale and the Functional Independence Measure for Children (WeeFIM) were used to assess cognitive and motor function respectively. The Western Neuro Sensory Scale Profile (WNSSP) was used to assess and monitor | |

(continued on next page)
| Source                        | Study Group                                                                 | Demographics and Clinical Characteristics                                                                 | Assessment Methods                                                                                                         | Key findings relating to Autonomic Dysfunction                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Sorek et al. (2018)           | **Assessment of cardiac autonomic control parameters in adolescents** with ABI in comparison with typically developed controls. | ABI group (n=17): Consisted of post-traumatic injury (n=10); post-encephalitis (n=2); post-brain tumour dissection (n=4) and post-arteriovenous malformation (n=1). Age: 15.4 years ± 1.19. Individuals were 3 months to 2 years post-injury. Age and gender matched control group (n=18): Age: 14.2 years ± 2.0. | Autonomic metrics (HR, SDNN and RMSSD) over a 5-minute recording period were captured using a heart rate monitor. Executive cognitive function was measured using the parent completed BRIEF questionnaire. | Poor outcomes of brain injury were associated with a higher autonomic dysfunction index in newborns and this association remained significant (P=0.041) even after adjusting for the encephalopathy grade. Following vagal stimuli, there were minimal changes in HR in newborns with impaired ANS. Assessment of HRV metrics can provide useful information regarding neurodevelopmental outcomes and add weight to the evidence that autonomic dysregulation can have a deleterious impact on routine interventions such as therapeutic hypothermia during neonatal care. Real-time continuous HRV analysis in those with autonomic dysregulation can be used to predict the risk for maladaptive outcomes to ongoing treatment in newborns with hypoxic-ischaemic encephalopathy. The pattern of brain injury was associated with the extent of autonomic dysregulation i.e. HRV. |
| Letzkus et al. (2018b)        | **Exploratory cohort study of 8 children examining the physical environmental factors impacting on PSH following brain injury.** | Eight (8) children aged between 5 weeks to 13 years of which 7 had nontraumatic brain injuries and 1 had a TBI. | Measurement of physical characteristics. Environmental stimuli were captured using the Environmental Assessment Form alongside a light and sound meter. Semi-structured interviews with parent/carers and with nurses. | There was no statistically significant association with PSH and the following variables: light, noise, positioning, persons, gown and head-of-bed elevation. Environmental factors could play an important role for the management of autonomic dysregulation in children following severe brain injury. |
| Campbell et al. (2018)        | **To assess whether autonomic dysregulation has a contributory role in the development of secondary brain injury in newborn infants with hypoxic-ischaemic encephalopathy undergoing therapeutic hypothermia.** | Newborns (n=25) with a gestational age (weeks) (mean ± SD): 38.1 ± 1.9. Infants were treated using therapeutic hypothermia for 72h. All infants had signs of moderate (n=20) to severe (n=5) encephalopathy. | Autonomic metrics (HRV) and other physiological data were measured using ECG, EEG, cerebral NIRS methodology and MRI. Thresholds of HRV metrics were used to categorize infants into those with an ‘impaired’ ANS and those with an ‘intact’ ANS. An autonomic dysfunction index defined as number of impaired 10-minute epochs (≥1 HRV metric beyond threshold) was estimated for each infant. | Poor outcomes of brain injury were associated with a higher autonomic dysfunction index in newborns and this association remained significant (P=0.001) when comparing the characteristics of children who did or did not transition to rehabilitation. Children with PSH status had a longer acute length of stay (P<0.024). The scales did not show any significant differences in cognitive, motor function or transition to rehabilitation between the PSH and non-PSH groups after controlling for age and type of brain injury. At rest, a higher HR was noted for adolescents in the ABI group (mean difference of 18.9 bpm 95% CI 9.8–28.0 bpm). Autonomic metrics such as SDNN and RMSSD were lower in the ABI group when compared to the control group (SDNN and RMSSD values mean difference of 21.6 ms 95% CI 9.0–34.3 and 19.5 ms 95% CI 7.3–31.7 ms, respectively). Cardiac autonomic control parameters should be monitored in young people for the assessment of longer-term outcomes post ABI. Temperature was found to be associated with PSH (P<0.02). The risk of PSH was increased with lower room temperatures (≤ 69°F). Blanket application was also associated with an increased risk of PSH (P=0.009). There was no statistically significant association with PSH and the following variables: light, noise, positioning, persons, gown and head-of-bed elevation. |
| Metzler et al. (2017)          | **Prospective study to characterise the association between HRV and brain injury in newborns following** | Data was analysed from 74 newborns with a gestational age (weeks) (mean ± SD): 38.7 ± 1.5. | Clinical and autonomic measurements were assessed using ECG and MRI. | Small changes in those who have not regained consciousness. |
Table 1 (continued)

| Source                              | Study Group                      | Demographics and Clinical Characteristics                                                                 | Assessment Methods                                                                 | Key findings relating to Autonomic Dysfunction                                      |
|-------------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Pozzi et al. (2017)                 | Retrospective observational cohort study in 26 pediatric patients with ABI to examine PSH following treatment during rehabilitation. | Patients were 8 ± 5.2 year at admission and followed for 3 years during their neurological rehabilitation. The clinical sample consisted of ABI caused by trauma (n=12); anoxia (n=9) or other causes (n=5). PSH data was analysed from 23 patients. Patients received several different drug treatments. | Description of treatment regimens Clinical features of PSH.                       | The clinical history of PSH was varied with 18 patients showing one cycle of PSH while others had relapses. After injury the remission from PSH was 116.9 ± 96.4 days. Amongst the enteral treatments, remission was more probable using diazepam (OR = 8.89, 95% CI = 3.37–23.44, P<0.001) followed by propranolol (OR = 1.22, 95% CI = 1.04–1.42, P=0.014) in comparison to baclofen doses (OR = 1.07, 95% CI = 0.88–1.29, P=0.497). The pathogenic nature of the traumatic ABI was also suggested to lead to a better chance of remission i.e. when compared to anoxic and non-traumatic (and non-anoxic ABI). |
| Al-Shargabi et al. (2017)           | Cohort study to measure the inflammatory cytokine response and HRV in 30 newborns with hypoxic-ischaemic encephalopathy undergoing therapeutic cooling. | Data was analysed from 30 newborns with a gestational age (weeks) (mean [min-max]): 39 (35, 40). Brain injury by MRI was classified as none (n=12), mild (n=6), moderate/severe (n=7) or died (n=5) before the MRI. All infants had moderate (92.8 %) to severe (7.2 %) encephalopathy. | Serum cytokine levels measured using electrochemiluminescence-based assay. Continuous ECG recording for HRV analysis. | The levels of certain inflammatory cytokines (IL-6, IL-8, IL-10, and IL-13) were inversely related (P<0.01) to specific HRV metrics. The study concluded that elevated levels of pro-inflammatory cytokines are associated with depressed HRV in newborns with hypoxic-ischaemic encephalopathy. The autonomic dysregulation could be caused by pro-inflammatory cytokine release triggered by the hypoxia-ischemia. Even though the cases had similar injuries, the severity of PSH in all three cases differed with Case 2 having mild PSH while Cases 1 and 3 had severe PSH. The thalamus was not affected in Case 2, however in cases with severe PSH, MRI imaging revealed substantial changes reflected as bilateral and symmetric damage to thalamic structures. |
| Mrkobrada et al. (2016)             | Case series in three paediatric patients who developed PSH following a hypoxic brain injury. | Case 1 (8-year-old boy) sustained a brain injury caused by accidental strangulation. Case 2 (8-year-old girl) had a brain injury caused by increased intracranial pressure following surgery for a brain tumour. Case 3 was a healthy 19-month-boy who following group infection sustained a hypoxic brain injury | MRIs of the brain                                                                 | (continued on next page)                                                             |
### Table 1 (continued)

| Source | Study Group | Demographics and Clinical Characteristics | Assessment Methods | Key findings relating to Autonomic Dysfunction |
|--------|-------------|------------------------------------------|--------------------|-----------------------------------------------|
| Farias-Moeller et al. (2015) | Evaluation of PSH in paediatric patients identified as having encephalitis and meningoencephalitis | 59 patients met the inclusion for encephalitis and separated into those with PSH in the non-bacterial encephalitis group (n = 17, age [min-max], 5 years [2–12]) and the bacterial meningoencephalitis group (n = 7, age [min-max], 5 years [0–11]). | Retrospective review of the electronic medical records | Damage to bilateral thalamus might be important for the symptom development in PSH and imaging of the thalamus following brain injury could be considered as a predictor for the severity and length of autonomic dysregulation in this case series. PSH was observed in 41 % of the patient population and was more frequent in the non-bacterial group. In the non-bacterial encephalitis group, female gender, history of seizures and/or fever on presentation were related to a higher frequency of PSH. Patients with PSH stayed longer in hospital compared to those without. The incidence of PSH in the cases series was about 11 % and the imaging studies revealed a picture of diffuse axonal injury in each case. PSH was noted to produce poorer clinical outcomes with regards to overall mortality, recovery time and developing other deleterious symptomatology such as risk of infections. Strict treatment guidelines for the management of autonomic dysregulation in the paediatric population following brain injury have not yet been established. In very preterm infants, perinatal neurological injuries could be connected to an impaired maturation of the ANS. This autonomic dysregulation may then further complicate the management of neurological symptoms. During the first 24 h after birth the likelihood of one or more negative outcomes increases for every 10ms decrease in HRV. Depressed HRV after birth during the first week and after rewarming from hypothermia was correlated with adverse outcomes of death and moderate to severe impairments of EEG and MRI outcomes. HRV monitoring can provide a useful non-invasive biomarker to monitor and track acute neurological dysfunction in newborn infants. |
| Deepika et al. (2015) | Case series in four paediatric patients with PSH following brain injury. | Case 1 (10-year-old girl) sustained a road traffic accident with a GCS of 4. Case 2 (6-year-old boy) had a TBI and on hospital admission his GCS was 4. Case 3 (6-year-old boy) had a TBI following a fall and had a GCS of 4. Case 4 (15-year-old girl) had a TBI following a road traffic accident with a GCS of 6. | Evaluation of PSH with MRI assessments and other clinical data. | |
| Thiriez et al. (2015) | To assess the impact of autonomic dysregulation on outcomes and rehabilitation in children with brain injury | Total infants (n=38): Normal neurological outcome (n=18) Impaired neurological outcome (n=20) | Polysomnography recordings and spectral waveform analysis to assess HRV autonomic metrics. | |
| Vergales et al. (2014) | To explore changes in heart rate characteristics with brain injury, EEG and MRI in neonates with acute perinatal hypoxic-ischaemic encephalopathy undergoing hypothermia. | Heart rate characteristics data were available for 67 neonates with moderate to severe hypoxic-ischaemic encephalopathy. Data was available for 37 neonates during the first 24 h after birth and 67 neonates had data available from days 2–7. Mean gestational age: 38.4 weeks ± 1.4 Birth weight: 2326 g ± 511 | HRV, EEG and MRI monitoring on first day after birth, after hypothermia and during rewarming (4–7 days after). | |
| Kirk et al. (2012) | Retrospective study assessing the impact of autonomic dysregulation in very preterm newborns deemed to be of high risk of neurological injury. | Dysautonomia group (n=33): Age, mean (SD): 11 years 4 months (6 years 1 month) Consisted of TBI (n=19); cardiac arrest (n=8); CNS infection (n=3); stroke (n=1) and neoplasm (n=2). No dysautonomia group (n=216): Age, mean (SD): 11 years 11 months (5 years 6 months) Consisted of TBI (n=176); cardiac arrest (n=18); CNS infection (n=7); stroke (n=10) and neoplasm (n=5). | Retrospective review of clinical records with autonomic dysregulation (dysautonomia). | Autonomic dysregulation was noted in 13 % of children with brain injuries and occurred in 10 % after TBI and 31 % after cardio-respiratory arrest. Amongst clinical signs, hypertension, diaphoresis, and dystonia best predicted the occurrence of autonomic dysregulation (dysautonomia). Children with dysautonomia had longer rehabilitation and poorer functional outcomes. |
| Hoang et al. (2012a) | A 10-year follow-up study of 43 patients with, impaired consciousness and autonomic dysregulation following severe TBI treated with intrathecal baclofen. | Patients were grouped according to Coma Recovery Scale–Revised (CRS-R) score according to consciousness levels: Group 1 (n=21) had maximal CRS-R score of 33, Group 2 (n=13) had a CRS-R score 0–22 and Group 3 (patients were grouped according to CRS-R score – 23 and had the best consciousness and recovery received intrathecal baclofen later than Group 2. This indicated a later onset of autonomic dysregulation in Group 1 when compared to Group 1. | Rating scales including the Coma Recovery Scale–Revised (CRS-R), Barthel Index (BI), the Ashworth scale and scoring of hypertonic and sweating episodes. | Retrospective review of patients' characteristics. |
Table 1 (continued)

| Source                  | Study Group                                                                 | Demographics and Clinical Characteristics                                                                 | Assessment Methods                        | Key findings relating to Autonomic Dysfunction |
|------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------|
| Hoarau et al. (2012b)  | To compare the long-term (about 10 years) functional outcomes of patients with severe TBI and hypoxic brain injury with autonomic dysregulation and hypertonia following intrathecal baclofen treatment. | Serum creatinine: 1.7 (1.2–2.8)纳mol/L, Mean (min-max) = 1.8 (1.2–2.8), Male: n = 86, female: n = 74 | Rating scales: CRS-R, BI, the Ashworth scale and scoring of hypertonic and sweating episodes. Retrospective review of medical history. | Patients with TBI showed a higher degree of longer-term improvements in conscious recovery (P < 0.001) and in activities of daily living (P < 0.008) than those with hypoxic brain injury. Autonomic dysregulation and hypertonia also improved in the TBI group in comparison to the hypoxic brain injury group. Those with hypoxic brain injury also required higher doses of intrathecal baclofen (P < 0.03). Even in the presence of intrathecal baclofen, when compared with patients with TBI, those with hypoxic brain injury had worse clinical outcomes with concomitant signs of autonomic dysregulation (dysautonomia). Functional recovery was not possible in those with hypoxic brain injury. Dysautonomia occurred with an incidence of about 20% in patients with severe TBI. Younger age, a low admission GCS score was associated with development of dysautonomia. The GCS score alone was not found to be a risk factor for the development of dysautonomia. The lower age and diffuse axonal injury were suggested to be independent risk factors for the prediction of dysautonomia. Diffuse axonal injury was observed in about 14% of patients. Multivariate analysis showed that dysautonomia (P < 0.018; OR = 4.17), hyperglycemia (≥ 8mmol/L [P < 0.001; OR = 3.84] on ICU admission) and subdural haematoma (P = 0.031; OR = 3.99) were associated with a higher rate of mortality in patients. The study suggests that when there is a diagnosis of diffuse axonal injury in patients with head injuries dysautonomia, hyperglycemia and subdural haematoma are risk factors associated with higher rates of mortality. |
| Lv et al. (2011)        | A prospective cohort study of patients with severe TBI followed up over a 2-year period to explore the clinical factors associated with autonomic dysregulation (dysautonomia). | Serum creatinine: 1.7 (1.2–2.8)纳mol/L, Mean (min-max) = 1.8 (1.2–2.8), Male: n = 86, female: n = 74 | Patients were prospectively observed clinically. All patients had head computed tomography and MRL. | Dysautonomia occurred with an incidence of about 20% in patients with severe TBI. Younger age, a low admission GCS score was associated with development of dysautonomia. The GCS score alone was not found to be a risk factor for the development of dysautonomia. The lower age and diffuse axonal injury were suggested to be independent risk factors for the prediction of dysautonomia. Diffuse axonal injury was observed in about 14% of patients. Multivariate analysis showed that dysautonomia (P < 0.018; OR = 4.17), hyperglycemia (≥ 8mmol/L [P < 0.001; OR = 3.84] on ICU admission) and subdural haematoma (P = 0.031; OR = 3.99) were associated with a higher rate of mortality in patients. The study suggests that when there is a diagnosis of diffuse axonal injury in patients with head injuries dysautonomia, hyperglycemia and subdural haematoma are risk factors associated with higher rates of mortality. |
| Chelly et al. (2011)    | A retrospective study of 124 cases to explore post-traumatic diffuse axonal injury on functional outcomes and mortality. | Serum creatinine: 1.7 (1.2–2.8)纳mol/L, Mean (min-max) = 1.8 (1.2–2.8), Male: n = 86, female: n = 74 | Retrospective review of medical records including clinical parameters brain MRI and EEG. | Dysautonomia occurred with an incidence of about 20% in patients with severe TBI. Younger age, a low admission GCS score was associated with development of dysautonomia. The GCS score alone was not found to be a risk factor for the development of dysautonomia. The lower age and diffuse axonal injury were suggested to be independent risk factors for the prediction of dysautonomia. Diffuse axonal injury was observed in about 14% of patients. Multivariate analysis showed that dysautonomia (P < 0.018; OR = 4.17), hyperglycemia (≥ 8mmol/L [P < 0.001; OR = 3.84] on ICU admission) and subdural haematoma (P = 0.031; OR = 3.99) were associated with a higher rate of mortality in patients. The study suggests that when there is a diagnosis of diffuse axonal injury in patients with head injuries dysautonomia, hyperglycemia and subdural haematoma are risk factors associated with higher rates of mortality. |
| Menteer et al. (2010)   | A case-controlled study in 7 patients with severe heart failure to explore changes in the CNS compared to age and gender matched healthy controls. | Serum creatinine: 1.7 (1.2–2.8)纳mol/L, Mean (min-max) = 1.8 (1.2–2.8), Male: n = 86, female: n = 74 | MRI brain scans. | Gray matter volume loss was noted in the heart failure group independent of cardiovascular disease. The authors noted that in heart failure patients, the gray matter volume loss was apparent in the (continued on next page) |
Table 1 (continued)

| Source | Study Group | Demographics and Clinical Characteristics | Assessment Methods | Key findings relating to Autonomic Dysfunction |
|--------|-------------|-------------------------------------------|--------------------|-----------------------------------------------|
| Katz-Leurer et al. (2010) | A comparative study measuring HRV in children with post-severe TBI to age matched control subjects, | Patients with TBI (males): n=12 (mean age [SD]): 10 years ± 3 | HRV parameters determined at rest and while walking on a treadmill. | brain regions that included the left and right insular cortices. These anatomical brain regions are associated with autonomic function and govern both sympathetic and parasympathetic outflow. Resting HR was higher in the TBI group when compared to the typically developed group (TBI group 91.8 ± 7.0 bpm vs. 72.0 ± 7.1 bpm in the healthy control group, P<0.05). This finding was mirrored during exercise (TBI group 123.4 ± 15.5 bpm vs 113.0 ± 9.1 bpm in the healthy control group, P<0.05). At the resting state the HRV metrics were lower in the TBI group when compared to typically developed controls. The study indicates that in children with severe TBI, the ANS is impaired and less functional compared to typically developed controls at rest and during exercise. PSH was observed in approximately 18% of patients with severe TBI. The age range of the PSH group was lower than the non-PSH group (25.9 years vs. 44.8 years). Those with PSH also had a much longer stay in ICU in comparison to patients without PSH (60.6 ± 50 vs. 23.0 ± 25, P<0.001). Brain imaging revealed damage to the brainstem in the PSH group and further supports the suggestion that damage to the brainstem is an indicator of poor functional outcome after severe TBI. Amongst the treatments used, gabapentin was effective in reducing the symptoms of autonomic dysregulation in two of the cases. Other medications used in the cases such as bromocriptine, metoprolol, sodium valproate and narcotic analgesics were not as effective in reducing the frequency or intensity of the autonomic storms. While reducing the severity of the autonomic storms, intrathecal baclofen did not reduce the frequency of them. In this study, the available evidence indicated that intravenous morphine, benzodiazepines, propranolol, bromocriptine and perhaps also intrathecal baclofen could be used to manage the dysautonomia. No clear treatment guidelines for the management of dysautonomia following severe TBI exists. The sympathovagal balance reflected by the LF/HF ratio decreased when the intracranial pressure was greater than 30 mm Hg (P<0.001) or the cerebral perfusion pressure was less than 40 mm Hg (P<0.001). There was no linear relationship between the LF/HF ratio with either the intracranial pressure or cerebral perfusion pressure. |
| Lv et al. (2010) | A prospective case control study during a 24-month period to identify the risk factors of PSH in 87 patients with severe TBI. | With PSH (n=16): Age (years, mean ± SD): 25.9 ± 10 GCS at admission (mean ± SD): 5.19 ± 1.22 Injury consisted of motor vehicle accident (n=13) or fall (n=3), Without PSH (n=71): Age (years, mean ± SD): 44.8 ± 18 GCS at admission (mean ± SD): 6.24 ± 1.49 Injury consisted of motor vehicle accident (n=46), fall (n=10) or other (n=15). | Clinical observations alongside brain MRI. | |
| Baguley et al. (2007) | Case study in examining the management of dysautonomia in 6 patients with severe TBI using gabapentin | Case reports ages were in their later teen or early twenties. Injury was due to road traffic accidents. | Clinical management using different treatment regimens. | |
| Baguley et al. (2004) | Retrospective case-controlled study in patients with severe TBI examining the management of dysautonomia using different drug treatments. | With dysautonomia (n=35): Age (years, mean: 20.5 GCS (median): 4.0 Injury consisted of motor vehicle accident (n=25) or other (n=10). Controls (n=35): Age (years, mean: 20.7 GCS (median): 3.0 Injury consisted of motor vehicle accident (n=22) or other (n=13). | Review of clinical files including CT scans and other physiological parameters. | |
| Biswas et al. (2000) | Prospective case series assessing HRV and outcomes in children with acute TBI. | Fifteen (15) children with acute TBI and 4 controls Age ranging from 7 months to 12 years. | HRV measurements and spectral analysis. Intracranial pressure and cerebral perfusion pressure measurements | |

(continued on next page)
3.4.2. Assessment of autonomic dysregulation

Brain injury increases the likelihood for the potential of neurological complications in children. The dysregulated autonomic functioning can be reflected in impaired autonomic metrics. The time-domain metric SDNN (Standard Deviation of all NN intervals) and the RMSSD (root mean square of successive differences) were found to be lower in adolescents with ABI (Sorek et al., 2018). When examining whether Heart Rate Variability (HRV) is associated with PSH severity in children with ABI, SDNN and RMSDD were lower in children with ABI when compared to typically developed controls.

Goldstein et al. (1996) A prospective clinical study to explore the autonomic control of heart rate in 37 children with acute brain injury. HRV spectral analyses Plasma catecholamine measurements

Meythaler and Stinson. (1994) Case series of three patients with severe TBI examining the management of centrally mediated fevers with propranolol. Brain scans to characterise the brain injury. Propranolol treatment.

Abbreviations: ABI (Acquired Brain Injury); ANS (Autonomic Nervous System); ASPECT (Alberta Stroke Program Early CT); BI (Barthel Index); BP (Blood Pressure); bpm (beats per minute); BRIEF (Behaviour Rating Inventory of Executive Function); CAD (Central Autonomic Dysfunction); CI (Confidence Interval); CNS (Central Nervous System); CRS-R (Coma Recovery Scale-Revised); ECG (Electrocardiogram); EEG (Electroencephalography); GCS (Glasgow Coma Scale); HF (High Frequency); HR (Heart Rate); HRV (Heart Rate Variability); ICC (Intensive Care Unit); LF (Low Frequency); MCA (Middle Cerebral Artery); MRI (Magnetic Resonance Imaging); ms (milliseconds); NIRS (Near Infrared Spectroscopy); OR (Odds Ratio); PSH (Paroxysmal Sympathetic Hyperactivity); R-R (Inter-beat interval); RLA (Rancho Los Amigos Scale); RMSSD (Root Mean Square of Successive Differences); sABI (Severe Acquired Brain Injury); SD (Standard Deviation); SDNN (Standard Deviation of all NN intervals); TBI (Traumatic Brain Injury); WeeFIM (Functional Independence Measure for Children) scale; WNSSP (Western Neuro Sensory Scale Profile).
In children, elevations in intracranial pressure following acute TBI can also shift the sympathovagal balance as reflected by the LF/HF ratio (Biswas et al., 2000). In these patients, a lower sympathovagal balance was associated with patients who progressed to brain death and supports the premise that the LF/HF ratio or other autonomic metrics could be used as a viable autonomic metric to identify those children who may have more favourable outcomes following acute TBI (Goldstein et al., 1996) or other neurological impairment.

Even at very early life stages assessing the symptoms of autonomic dysfunction using autonomic metrics cannot be understated. In newborn infants with hypoxic-ischaemic encephalopathy, poor outcomes of brain injury were linked to greater autonomic dysregulation and remained significant even after adjusting for the severity of the encephalopathy (Campbell et al., 2018). The findings from this study echoed that of a previous study in newborns and using spectral analysis showed that the relative Low Frequency power (a measure of autonomic outflow) was negatively associated with brain injury caused by hypoxic-ischaemic encephalopathy (Metzler et al., 2017). Indeed, in this patient...
population, depressed HRV after birth was associated with poorer functional outcomes as indicated by electroencephalography (EEG) and Magnetic Resonance Imaging (MRI) parameters (Vergales et al., 2014).

3.5. Theme C: Treatment of Autonomic Dysregulation

When evaluating the treatment regimens to manage autonomic dysregulation in severe brain injury, intrathecal baclofen improved the symptoms of autonomic dysregulation following severe TBI (Pucks-Faes et al., 2018). Patients with severe TBI and higher Coma Recovery Scale scores also appeared to require lower doses of intrathecal baclofen and the autonomic dysregulation could be managed more effectively in this group (Hoarau et al., 2012a). However, when compared with patients with severe TBI, in patients with hypoxic brain injury, intrathecal baclofen was not as effective, and these patients had worse clinical outcomes and poor functional recovery (Hoarau et al., 2012b). It is possible that following diffuse axonal injury arising from brain trauma; neurons still have enough integrity that allows them to respond to baclofen treatment in comparison to injury resulting from hypoxia where the neurons necrose and would no longer be able to effectively respond to treatment (Adams et al., 2000). Another study showed that in 23 children with PSH following ABI, remission of autonomic dysregulation was the highest using diazepam followed by propranolol but the lowest with enteral baclofen (Poźni et al., 2017). These findings support earlier observations that intravenous propranolol and perhaps also intrathecal baclofen amongst other medications could be used to manage autonomic dysregulation (Baguley et al., 2004). In some other instances where the brain injury causes hyperthermia due to a hypothalamic injury caused by the TBI, propranolol can be used to control the fever and manage temperature changes (Meythaler and Stinson, 1994) that are frequently associated with autonomic dysregulation. In one other study that assessed HRV in 16 term newborns with unilateral middle cerebral artery strokes, phenoxybarbital was shown to increase sympathetic but decrease parasympathetic tone, and negatively affected the sympathovagal balance (Reich et al., 2019).

4. Discussion

Understanding the organic features of paediatric brain injury against the background of autonomic dysfunction is critical to gathering a deeper awareness of how the dysregulation impacts on neurological outcomes and whether there is improved rehabilitation and recovery. What is clear from the themes is that the neurological outcomes following brain injury in children are highly heterogeneous. This study specifically focused on autonomic dysregulation arising from brain injury in children. The prominent themes that emerged are those that stressed the importance of recognising clinical signs, using appropriate treatment to manage autonomic sequelae and how the consequent autonomic dysregulation can lead to worse functional outcomes. This raises the question of whether the three identified themes (A) The Recognition of Autonomic Dysregulation (i.e., what to look for?) (B) Possible Mechanisms and Assessment of Autonomic Dysregulation (i.e., why? and how to assess) and (C) Treatment of Autonomic Dysregulation (i.e., what to do?) are useful to inform everyday clinical practice when treating patients with RTT. In attempting to address this, the clinical impact of these themes is best explained by addressing the following questions:

1. Can early recognition of clinical symptoms assist in managing the autonomic dysregulation seen in Rett Syndrome?
2. Can depressed HRV be used as a biomarker to predict the long-term outcomes of autonomic dysregulation in Rett Syndrome?
3. What is the impact of the disruption of catecholamine release and an increase in pro-inflammatory cytokines on EBAD in Rett patients?

4.1. Can early recognition of clinical symptoms assist in managing the autonomic dysregulation seen in Rett Syndrome?

The trajectory of autonomic dysregulation, especially from a developmental perspective, is significantly understudied in RTT. Our previous evidence synthesis showed that the dysmaturated of neuronal networks in Rett patients affects the electrical stability of the cardiovascular system and other neurochemicals as well as how the brainstem regulates breathing (Singh et al., 2020). Managing the autonomic dysregulation at earlier stages of the disorder would improve the longer-term outcomes of these patients and reduce the overall burden of RTT. As indicated by the themes, in childhood brain injury, the primary damage can cause additional secondary complications that can drastically affect patient survival. Other evidence suggests that nearly 80 % of the autonomic storms that manifest in patients with autonomic dysregulation following brain injury occur due to external stimuli (Fernández-Ortega et al., 2012; Baguley et al., 2009). This autonomic picture is mirrored in Rett patients, whereby the autonomic dysregulation seen in these patients complicates the symptoms and how they present clinically. Secondary symptoms such as stress, physical problems including seizures, pain etc. can all exacerbate the symptoms of behavioural, emotional and autonomic dysregulation in RTT (Singh and Santosh, 2018). The findings from the present study do not allow us to generalise what impact the secondary symptoms will have on patient outcomes in RTT, especially in terms of the development of autonomic dysregulation from childhood to adulthood. It is plausible, however, that in young children with RTT, the ANS might be more sensitive to changes given that it is particularly vulnerable during early life stages. Even though it has been suggested that the vagal nerve functions mainly after birth (Porges and Furman, 2011), it is possible that dysregulation of Brain Derived Neurotrophic Factor (BDNF) in Rett patients could activate this branch earlier. Brain maturation will significantly influence the prognosis of autonomic dysregulation seen following a brain injury and in patients with RTT.

Like the autonomic dysregulation observed in RTT, in paediatric brain injury, the dysregulation also presents with a constellation of symptoms. In children with brain injury, the factors that affect recovery and transition to rehabilitation are the age of the patient, medications to stimulate arousal, use of venous, respiratory and feeding devices, hyperglycaemia on ICU admission, hypertension, diaphoresis, and dystonia. There are metabolic disturbances with abnormal carbohydrate metabolism in patients with RTT (Kyle et al., 2018) and despite case reports (Akin et al., 2012), hyperglycaemia is not a frequent finding in the RTT population. Other factors also seem to affect risk, such as environmental temperature and blanket application. Some other evidence has revealed that elements such as constipation, skin wounds (bed sores), tight clothing and cold tube feeding tubes were found to be possible triggers of autonomic dysregulation arising from brain injuries in children (Burton and Morozova, 2017). Furthermore, a retrospective cohort study in children with TBI showed that the triad of hypertension, diaphoresis, and dystonia was the most useful in predicting a diagnosis of autonomic dysregulation in these children (Kirk et al., 2012). It is difficult to reconcile, however, given the scarcity in the literature regarding the clinical signs of autonomic dysregulation in Rett children whether these would appear alone or in combination. Nevertheless, these clinical signs and symptoms would all be of relevance in RTT and pro-actively monitoring the signs of HRV, preventing bed sores in bed-bound patients, avoiding tight clothing, ensuring that room temperature is not too low alongside recognising the signs of diaphoresis, and dystonia would be useful to reduce the problematic symptoms of autonomic dysregulation and hence assist in the management of EBAD.

Despite these factors, in Rett patients, probably the most critical step when managing the autonomic dysregulation would be to determine
what clinical signs and symptoms are ones that need to be recognised and addressed most urgently. Respiratory, cardiac and skeletal problems are of major concern in Rett. There are more than a dozen breathing phenotypes (Tarquinio et al., 2018) in Rett, and some of these phenotypes might be more vulnerable than others (Singh et al., 2020; Mackay et al., 2017). The sporadic nature of epilepsy is also a worrying concern (Tarquinio et al., 2017). Despite these discrepancies, the overall clinical impression adds support to the argument that even though the management of the autonomic dysregulation is complicated in Rett due to the divergent symptomatology, early recognition of the clinical signs and symptoms mentioned above would be of benefit when managing autonomic dysregulation in the Rett population.

4.2. Can depressed HRV be used as a biomarker to predict the longer-term outcomes of autonomic dysregulation in Rett Syndrome?

The evidence synthesis showed that following brain injury, an autonomic dysregulation occurs in the ANS. This dysregulation is reflected by changes in autonomic metrics and is supported by observations that in children with brain injury, the sympathovagal balance reflected by the LF/HF ratio is significantly shifted. It is unclear from the available evidence whether the shift predominantly rectifies to a more dominant sympathetic or parasympathetic profile in children with brain injury. From an autonomic metric viewpoint, there are however, similarities and differences in the autonomic dysregulation arising from brain injury and Rett. First, the LF/HF ratio is higher in children with brain injury (Kim et al., 2017) and second in adolescents with ABI the HRV metrics SDNN and RMSSD are depressed (Sorok et al., 2018). This autonomic profile aligns with that seen in patients with Rett (Singh et al., 2020).

The evidence synthesis also showed that the LF power was negatively associated with the pattern of brain injury in newborns (Metzler et al., 2017) and poor functional outcomes were associated with a higher autonomic dysfunction index in newborns even after adjusting for the encephalopathy grade (Campbell et al., 2018). In newborns with acute perinatal hypoxia, it was also shown that during the first 24 h after birth the likelihood of one or more adverse outcomes increases for every 10 ms decrease in HRV (Vergales et al., 2014). We have previously suggested that the autonomic profile in RTT mirrors that of preterm infants (Singh et al., 2020) and taken together these observations indicate that depressed HRV might be useful in predicting the outcomes of autonomic dysregulation even at very early life stages. Given that detecting autonomic dysregulation is critical for improving longer-term outcomes in Rett patients, it raises the obvious question of what stage of the disorder can depressed HRV metrics provide clinically meaningful information.

It is likely that foetal reprogramming of MECP2 in Rett causes BDNF dysregulation, and the consequent autonomic dysmaturatation affects brain regions such as the Kolliker-Fuse and solitary tract (Singh et al., 2020). After birth, the ANS is developmentally immature. During the pre-regression phase of RTT, there is most likely to be a period of autonomic quiescence, and the subtle developmental changes that occur during this period will go undetected. The fluid plasticity of the developing brain allows MECP2 to bind to different post-natal methylated sites in neurones as the brain matures (Lavery and Zoghbi, 2019), however, in RTT the abnormal cytosine methylation (Connelly et al., 2020) in brain regions allows the network plasticity to sufficiently deteriorate so that the characteristic symptoms of Rett emerge.

During early post-natal brain development, further methylation checkpoints are missed, and as this transcriptional restraint is lost, the resulting altered neuronal gene expression drives the varied clinical symptoms seen at different developmental stages in Rett patients. Based on this presumption, it would, therefore, seem that measuring HRV metrics would only be useful when enough methylated checkpoints are missed in the developing brain, i.e. when the NGOr/SMRT corepressor complex can no longer be recruited (Tillotson et al., 2017; Lyst et al., 2013) to the methylated sites by MECP2 and symptoms of EBAD such as autonomic dysregulation first emerge. However, the clinical picture would be further complicated because, given the mutational landscape of Rett patients, the relative contribution that MECP2 has on methylated checkpoints within neuronal DNA in different parts of the developing brain is likely to be different between patients. This means that the symptoms of autonomic dysregulation emerge at different epochs.

Non-invasive wearable sensor technology to track autonomic dysregulation is useful for the management of EBAD symptoms in patients with RTT. While the use of this sensor technology needs to be validated in other clinical settings, measurement of autonomic metrics such as HRV and electrodeural activity (EDA) using wearable sensors are well tolerated by individuals with RTT and being small and non-intrusive can be managed quite easily with minimal distress to the patient. Monitoring EDA would be important to provide an assessment on the sympathetic component as the EDA reflects mainly the sympathetic activity (Dawson et al., 2008). Using EDA, children with autism have also been shown to have an abnormal sympathetic profile (Panju et al., 2015). Our previous work has shown that medicines such as buspirone and propranolol can assist in the management of EDA variability in Rett girls (Singh and Santosh, 2017; Santosh et al., 2016). From a clinical standpoint, we recommend that following a clinical diagnosis of RTT, the assessment of autonomic metrics using non-invasive wearable sensor technology should be adopted to measure depressed HRV metrics so that the longer-term outcomes of autonomic dysregulation can be monitored. In addition, assessment of EDA measures would be useful in the context of providing valuable information concerning the physical deterioration of the patient because the tonic measure of EDA can provide useful information concerning sympathetic arousal over longer time periods while phasic measures reflect reactivity and adaptation of the sympathetic profile during shorter periods (McCormick et al., 2014). It is unlikely that depressed HRV metric(s) and/or EDA parameters can be used as universal biomarkers. As the DNA methylation landscape of neurons is dramatically reconfigured in RTT during development, the autonomic profile between patients will be varied. However, we speculate that depressed HRV metrics alongside tonic and phasic measures of EDA might be better suited towards a personalised medicine approach in subsets of Rett patients. Such patient groups could be those with a more explicit mutational profile such as hypomorphic or complete loss of function mutations (Lavery and Zoghbi, 2019). Further work in these patient groups would be needed to confirm this hypothesis.

4.3. What is the impact of the disruption of catecholamine release and an increase in pro-inflammatory cytokines on EBAD in Rett patients?

The evidence extracted from the themes showed that disruption of catecholamine release and an increase in pro-inflammatory cytokines are associated with autonomic dysregulation. In newborns with hypoxic brain injury, inflammatory cytokines levels were inversely related to HRV metrics (Al-Shargabi et al., 2017) and plasma catecholamine levels are lower in children with acute brain injury (Goldstein et al., 1996). In Rett patients, we have previously suggested that infections and sepsis are triggers for EBAD (Singh and Santosh, 2017) and these factors can also have adverse outcomes on cardiac instability that could lead to a precipitous chain of events (Singh et al., 2020). Even though the number of studies that comprised this theme is small, it is highly likely that autonomic dysregulation exacerbates the inflammatory state in Rett patients. This is supported by the following observations: (I) Rett patients with Stage II, and clinical variants of RTT persist in a subclinical inflammatory state (Cartelazzio et al., 2014, 2017) and (II) recent evidence shows increased levels of pro-inflammatory proteins in the serum of Rett patients (Pecorelli et al., 2020). Some have suggested that following brain injury, the blood-brain barrier breaks down and allows circulating pro-inflammatory cytokines to enter the brain, causing secondary complications (Khalid et al., 2019).

In our previous work, we have indicated that in RTT, the central autonomic dysfunction causes disturbances in vagally mediated tone
(Singh et al., 2020). This is important in the context of inflammation since the vagal nerve has an important role in regulating the activation of pro-inflammatory mediators (Zila et al., 2017). It could, therefore, be reasoned that in RTT because of the underlying central autonomic dysfunction, this restraint is lost, and patients are more susceptible to infection and inflammation. Previous evidence has shown that amongst 57 patients with RTT who died, infection of the lower respiratory tract (36.8 %) followed by aspiration/asphyxiation (31.6 %) was the most frequent cause of death (Anderson et al., 2014). Another study that followed patients with RTT over a 30-year period, showed that the main cause of mortality was pneumonia (57.9 %) (Sarajlija et al., 2015). Although evidence is limited, one study using high resolution imaging has demonstrated an unrecognised lung disease in 27 individuals with classical RTT (De Felice et al., 2010). Some other work has shown that following surgery for scoliosis, children with RTT are at higher risk of respiratory complications when compared to children with cerebral palsy (Cohen et al., 2019). In cerebral palsy, poor mobility has also been linked to a higher risk of hospitalisation for respiratory complications (Blackmore et al., 2016; MacKay et al., 2018). This finding mirrors the observation in RTT, where respiratory morbidity has a significant impact on the quality of life of these patients (Halbach et al., 2013). The associated comorbidities such as scoliosis which can impede respiratory function, aspiration and impaired oromotor regulation can also exacerbate the risk of respiratory infection in patients with RTT (MacKay et al., 2018). When viewed together, brainstem immaturity, the associated dysfunction of respiratory networks, an underlying pulmonary vulnerability together with associated comorbidity probably makes this patient group more susceptible to respiratory complications such as airway infections.

Monitoring of HRV and EDA metrics would be useful in this instance because HRV vagal mediated changes can also be used to detect the initial signs of infection (Sullivan et al., 2014) and in RTT the changes in these metrics could provide useful information before a clinically recognised infection. Given the failure of animal models of RTT to recapitulate the symptoms seen clinically, we stress the over-generalisation of findings from animal models. Notwithstanding these concerns, a study has shown that loss of function of MECP2 causes the increased activation of NF-κB signalling and by decreasing this signalling in Mecp2-null mice the lifespan of these mice was extended (Kishi et al., 2016). When viewed together, the central autonomic dysregulation coupled with the abnormal activation of NF-κB in RTT could increase the risk of infection and sepsis in these patients. Clinical studies in this area are however incomplete and more evidence is needed to assess what impact autonomic dysregulation has on the sub-clinical inflammatory state and whether this heightens the risk of infections and sepsis in these patients.

The association between autonomic dysfunction and inflammation is bidirectional (Suzuki and Nakai, 2016). Although autonomic dysregulation may trigger inflammation through a network of circuits the opposite may also be true in RTT patients. Some other work has suggested that inflammatory markers might directly affect brain structures responsible for autonomic control (Tracey, 2002). The precise nature of how inflammation might favour autonomic dysregulation is uncertain and other mechanisms are probably also important such as the role of locally made mediators in the brain. It is plausible in RTT that the altered inflammatory state disrupts the neuroimmune axis leading to the progression of autonomic dysregulation. Further work would be needed to test this hypothesis to examine the neural-immune imbalance in this patient group.

4.4. What can we do to treat the autonomic dysregulation and hence manage EBAD?

The findings from brain injury patients suggest that the management of the autonomic dysregulation requires a multimodal treatment model that harnesses both environmental modifications and differential treatment regimens. The themes highlight the use of β-adrenergic blockers (propranolol), neumomodulators (bromocriptine, gabapentin, baclofen), barbiturates and benzodiazepines to manage the autonomic dysregulation and to improve the probability of remission in these patients. Other treatments include the use of α2 agonists (clonidine) and opioids (morphine) (Meyfroidt et al., 2017). None of the treatments can manage all the symptoms effectively, however some might be more effective in managing specific symptoms. Clonidine was useful in lowering heart rate and blood pressure but less efficient in managing temperature fluctuations (Meyfroidt et al., 2017; Rabinstein and Benarroch, 2008). Propranolol improved the survival in elderly patients following TBI, but no information about longer-term functional outcomes was provided (Ley et al., 2018). An earlier study showed that acute intravenous propranolol can be used to manage symptoms post head injury in some patients (Chiolero et al., 1989). In another instance, a combination of drugs is to be trialled to explore whether combined propranolol and clonidine might be more suitable in reducing the sympathetic outflow and the number of days spent on a ventilator following TBI in ICU patients aged 16–64 years of age (Patel et al., 2012). Other studies done in children with ABI have shown that remission of autonomic dysregulation was more probable with diazepam (Pożni et al., 2017) and the most useful treatments to manage PSH events were clonazepam, hydroxyzine, and delorazepam (Pożni et al., 2015). More recently, a single case study has shown that combined treatment with propranolol and dexmedetomidine was useful in attenuating the frequency of PSH in an 8-year-old child following TBI (Branstetter et al., 2020). Although not formally studied in children, a small pilot study has also shown improved outcomes in working memory following guanfacine treatment in adults 1 month after mild TBI (McAllister et al., 2011).

Yet despite the wide use of treatment regimens even in patients with brain injury, the treatment model for autonomic dysregulation is mostly speculative, and administration of treatment regimens are based on local experiences rather than objective evidence (Meyfroidt et al., 2017). There is also no evidence-based model providing a treatment plan for autonomic dysregulation following brain injury in children. Some authors have provided a clinical algorithm for the management of autonomic dysregulation in the paediatric (Burton and Morozova, 2017) or the general population (Samuel et al., 2016) after brain injury but neither of these clinical algorithms has been validated in other settings. At present, there is neither a standardised clinical algorithm for the management of autonomic dysregulation in patients with RTT. There is some overlap between the treatments used to manage the features of autonomic dysregulation that can be gleaned from patients with brain injury. We have previously shown that propranolol can be used to target the autonomic component of EBAD in RTT patients (Santosh et al., 2016) and in instances where a drug with a potential pro-arrhythmic risk is used, propranolol might be an option to use to lower the risk (Singh et al., 2020), however, there is no clear indication for the use of propranolol in patients with RTT and further assessment of its use in other clinical settings would be needed. It should be noted that due to the wide-ranging symptoms, not all treatments for autonomic dysregulation arising from brain injury would be applicable in the Rett population given the unwanted side effects, for example, the risk of sedation when using benzodiazepines or neuromodulators such as baclofen. It would also be important to check whether the medications used to treat the signs and symptoms of EBAD in RTT would mask some of the other stressors of autonomic dysregulation such as constipation and irritability (Burton and Morozova, 2017). In summary, while the recognition of clinical symptoms of autonomic dysregulation will be of benefit for the management of EBAD in Rett patients especially in the younger age group, the lack of a validated clinical algorithm of autonomic dysregulation hinders the early recognition and treatment of it in the RTT population and pro-active management of patient outcomes.

5. Conclusion

The goal of this review was to explore whether studies that evaluated the organic features, treatment and management of autonomic dysregulation in children with brain injury could inform our understanding of autonomic dysregulation in patients with RTT. Based on the findings
presented in this review the following conclusion was reached: Studies of autonomic dysregulation in paediatric brain injury do provide valuable information on the recognition, treatment and clinical management of autonomic dysregulation in patients with Rett. The main findings from this evidence synthesis are presented in Table 2. This study, for the first time, bridges the gap in knowledge regarding the outcomes of autonomic dysregulation from the perspective of brain-injured children and how it can lead to the development of application protocols in RTT. Management of EBAD in Rett patients is clinically challenging. Still, our evidence synthesis from data available in children with a brain injury has provided much-needed understanding and raised awareness of the underpinnings of autonomic dysregulation and its impact on longer-term outcomes in RTT. Monitoring of depressed HRV metrics alongside EDA and recognising the signs of diaphoresis and dystonia are all useful. Reducing the risk of bedsores, avoiding tight clothing and ensuring that room temperature is adequate would also be of benefit. The key clinical and research implication for patients with RTT are summarised in Fig. 3. While the emergence of themes and the extrapolation of information from children with brain injury should not be treated as being definitive, when viewed through the lens of RTT, we show that early recognition of these clinical symptoms and monitoring of autonomic metrics in Rett patients could assist in the development of a much-needed clinical model to treat autonomic dysregulation in this vulnerable patient group. The use of non-invasive wearable sensor technology for the assessment of autonomic metrics would also be sharable across clinical settings, however, these tools would need to be appropriately evaluated and validated.

Even though a personalised medicine approach is warranted, perhaps not surprisingly, the present study raises an important number of clinical questions that require further investigation. The inherent autonomic dysregulation has a profound impact on the emergence of secondary symptoms. There is, however, no standardised treatment algorithm for these secondary symptoms and in Rett patients, the level of evidence that favours one treatment option for another is low. A multimodal treatment approach is warranted. Monitoring of autonomic metrics could be used alongside other adjunct approaches such as using brain-enriched microRNAs to help classify patient groups and predict treatment response in RTT (Sheinerman et al., 2019).

While this study addresses the importance of managing autonomic dysregulation, it is clear from the evidence that the dysregulation is itself not the only nor the major challenge in the clinical management of RTT. The management of other comorbidities such as epilepsy, breathing problems, scoliosis, movement disorders, and feeding impairment also pose significant challenges in the clinical management. Furthermore, autonomic dysfunction cannot explain the natural history and phenotype of RTT across the lifespan. Even when patients’ profiles have been based on genotype-phenotype findings, the severity of comorbid symptoms can be highly variable (Halbach et al., 2012) suggesting that a wide-ranging approach to manage the broad symptom profile in RTT is needed.

6. Limitations

The purpose of this review was not to present an exhaustive list of treatment recommendations for autonomic dysregulation in Rett. From the perspective of brain injury, this area has previously been covered elsewhere (Burton and Morozova, 2017; Meyfroidt et al., 2017; Samuel et al., 2016; Baguley et al., 2004). Furthermore, while aspects of paediatric rehabilitation following brain injury have been covered (Camore et al., 2012), in the context of RTT, this is not entirely applicable. While criteria for PSH have been developed for acquired brain injury (Baguley et al., 2014; Perkes et al., 2011), there are no formal diagnostic criteria for the management or recognition of autonomic dysregulation in RTT. Despite these discrepancies, the recognition of clinical signs and risk factors of autonomic dysregulation identified in the present study would prove beneficial for the medical management of autonomic dysregulation in Rett patients. The term paroxysmal sympathetic hyperactivity (PSH)

Table 2

| Recognition | Rett Syndrome |
|-------------|--------------|
| **Sympathetic storming:** | 1 Sympathovagal imbalance |
| | Depressed HRV metrics |
| | Increased HR |
| Diaphoresis | Increased HR |
| Pupillary dilatation | Following diagnosis, assessment of autonomic metrics to measure depressed HRV metrics alongside EDA to predict functional outcomes should be considered. This might be more suited to subsets of Rett patients. |
| Constipation | Symptom profile is very similar: |
| Hypertension | Diaphoresis and dystonia should be managed better. |
| Hyperopia | Given the sensory issues and its risk in increasing EBAD, close attention should be paid to sensory factors such as skin wounds (bed sores), tight clothing and cold tube feeding tubes. |
| Sensory factors: | |
| - bed sores | |
| - tight clothing | |
| - environmental temperature | |
| Hyperglycaemia | |
| | **Damage to brain region:** |
| | There is likely to be brainstorm, thalamic and hypothalamic involvement in RTT. |
| | |
| | Disordered neurotrophic maturation of brainstem networks result in brainstorm vulnerability. |
| | Propranolol can be one option to use in managing the autonomic dysregulation. |
| | Alpha 2 agonists maybe candidates that need to be tested in clinical trials. |
| | |
| | Medicines such as gabapentin, baclofen, barbiturates, benzodiazepines and morphine have multi-system side effects which makes it difficult to use in patients with RTT. |
| | |
| | Medications that might have a detrimental effect on autonomic dysregulation such as p-adrenergic blocker induced hyperglycaemia or constipation with morphine for the treatment of pain should be monitored closely. |

*Sympathetic storming can represent in a myriad of different terms that are used to reflect autonomic dysregulation. For brevity a descriptive label has been used.

Based on the evidence synthesis. Other neuroanatomical areas are also likely to be involved.

There is no standardised clinical algorithm for the management of autonomic dysregulation.

Notes: The outcomes of autonomic dysregulation in patients with RTT and in those with paediatric brain injury are variable. While both patient groups present with a constellation of symptoms, common features and possible risk factors for autonomic dysregulation are mentioned for both groups. The extrapolation of information from children with brain injury, however, should not be treated as being definitive and the information presented for RTT should only be used as a guide.

Abbreviations: EBAD (Emotional, Behavioural and Autonomic Dysregulation); EDA (Electrodermal Activity); HR (Heart Rate); HRV (Heart Rate Variability); RTT (Rett Syndrome).
was first suggested in 2010 (Perkes et al., 2010) and has been used in the literature as a unifying term when describing the autonomic dysregulation in studies featuring brain injury (Baguley et al., 2014). In the context of reviewing studies and clinical trials relating to changes in the ANS in patients with RTT (Singh et al., 2020; Singh and Santosh, 2018) and for the purposes of the present article we have used the term autonomic dysregulation. It is quite possible that the search terms we have used could have missed some studies explicitly relating to PSH. However, we sought to limit the subjectivity of the search process by following published PRISMA guidelines to identify and select articles, have definable eligibility criteria and used two authors to independently perform the searches. Furthermore, the eligible articles that were analysed and the thematic analysis that followed were based on a consensus agreement between all the authors. Nevertheless, given our prior knowledge in this area, we are aware that some of the opinions formed in this review to a certain extent would be based on the subjective opinion of the authors.

While the review was focused on studies on paediatric brain injury, a few of the articles analysed had a mixed population or had patients with a wide age range (Pucks-Faes et al., 2018; Hoanzu et al., 2012a; Hoanzu et al., 2012b; Lv et al., 2011). The retrospective nature of some of the included studies (Pozzi et al., 2019; Pucks-Faes et al., 2018; Letzkus et al., 2018a; Pozzi et al., 2017; Kirk et al., 2012; Chelly et al., 2011; Baguley et al., 2004) also suggest that the prevalence of autonomic dysregulation is probably under-reported in these studies and how the dysregulation was managed is also likely to vary because the diagnosis was based on clinical judgement by the primary care team. This variability makes it challenging to form comparisons between studies, but despite these concerns, the eligible articles formed an essential part of the themes that emerged.

Authors’ contributions

JS formulated the idea of the systematic review, designed the study, drafted and wrote it. Both JS and EL blindly and independently performed the database searches for the eligible articles. JS and EL were involved in qualitative thematic analysis. Both EL and PS reviewed the manuscript for intellectual content and all authors revised the draft versions, read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

These can be obtained from the corresponding author.

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Declaration of Competing Interest

PS is the Principal Investigator (PI) on the Sarizotan (Protocol Number Sarizotan/001/II/2015; ClinicalTrials.gov Identifier: NCT02790034), GW Pharma (Protocol Number: GWND18064) and Anavex Life Sciences Corp. (Protocol Number: ANAVEX2–73-RS-002) clinical trials in patients with RTT.

PS is the co-inventor of the HealthTracker™ and is the Chief Executive Officer and shareholder in HealthTracker™.

JS was a Trial Research Methodologist on the Sarizotan Clinical Trial (Protocol Number Sarizotan/001/II/2015; ClinicalTrials.gov Identifier: NCT02790034) in patients with RTT.

EL has no competing interests to declare.

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Fig. 3. Clinical and Research Implications for the Management of Autonomic Dysregulation in Patients with Rett Syndrome. Abbreviations: EDA (electrodermal activity)
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