Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder


Abstract

Aim—To investigate breathing rhythm and brain stem autonomic control in patients with Rett disorder.

Setting—Two university teaching hospitals in the United Kingdom and the Rett Centre, Sweden.

Patients—56 female patients with Rett disorder, aged 2–35 years; 11 controls aged 5–28 years.

Design—One hour recordings of breathing movement, blood pressure, ECG R-R interval, heart rate, transcutaneous blood gases, cardiac vagal tone, and cardiac sensitivity to baroreflex measured on-line with synchronous EEG and video. Breathing rhythms were analysed in 47 cases.

Results—Respiratory rhythm was normal during sleep and abnormal in the waking state. Forced and apneustic breathing were prominent among 5–10 year olds, and Valsalva breathing in the over 18 year olds, who were also most likely to breathe normally. Inadequate breathing peaked among 10–18 year olds. Inadequate and exaggerated breathing was associated with vacant spells. Resting cardiac vagal tone and cardiac sensitivity to baroreflex were reduced.

Conclusions—Labile respiratory rhythms and poor integrative inhibition in Rett disorder suggest brain immaturity. Linking this to an early monoaminergic defect suggests possible targets for the MECP2 gene in clinical intervention. Exaggerated and inadequate autonomic responses may contribute to sudden death.

(Arch Dis Child 2001;85:29–37)

Keywords: Rett disorder; autonomic system; brain stem; dysautonomia

Rett disorder, causing profound intellectual and physical disability, is caused by MECP2 mutations.1,2 Of 56 classic British cases tested, 47 (87%) are mutation positive. There is a wide range of clinical severity.3,4 The prevalence of the disorder in the United Kingdom exceeds 1 in 10 000 of the female population.5

Autonomic manifestations include agitation, flushing, pupillary dilatation, and cold extremities relieved by sympathectomy.6 Disrupted sleep staging suggests an early monoamine deficit.7 Immaturity is suggested by an infantile distribution of the forebrain circulation8,9 and raised serotonin receptor binding in brain stem nuclei.10 Irregular breathing in the waking state is associated with non-epileptic vacant spells.11 Low resting cardiac vagal tone and weak vagal response to hyperventilation and breath holding suggest inadequate parasympathetic control.12

Our aim in this study was to characterise the abnormalities of respiratory rhythm and investigate the central autonomic competence in Rett disorder.

Methods

Subjects

Fifty six subjects were referred for diagnostic assessment. Control values came from 11 female volunteers and from previous studies.12–14 Parents received written explanations of procedures and results and provided consent. The ethics committee at South Glasgow University Hospitals NHS Trust approved the study. Rett subjects had all the classic criteria,15 except as follows: no decline in occipitofrontal circumference (n = 6); stagnation in development without regression (n = 4); and seizures before regression (n = 4).

Procedures and analyses

The subjects sat comfortably with carers while information was obtained by clinical examination and from case records, health questionnaires, and one hour continuous, synchronous, non-invasive autonomic and respiratory monitoring, time locked with video and EEG.

A stretch sensitive resistance plethysmograph at xiphiernal level recorded the amplitude of thoracic and abdominal breathing movements in arbitrary units. A TCM3 monitor (Radiometer, Copenhagen, Denmark) recorded partial pressures of oxygen (PO2) and carbon dioxide (PCO2) transcutaneously. A finger photoplethysmograph (FinapresTM, Ohmeda, USA) recorded digital arterial blood pressure in waveforms for calculation of beat by beat systolic, mean, and diastolic blood pressure. The central autonomic (brain stem) control of cardioinhibitory activity was monitored by the NeuroScope™ (MediFit Diagnostics, London, UK), which calculates cardiac vagal tone from ECG R-R intervals.16 The cardiac vagal tone is expressed in arbitrary units on a linear vagal scale.17

Breathing movements, levels of blood gases, and blood pressure waveforms were transmitted through an interface—the MedullaLab (MediFit Diagnostics)—and joined the NeuroScope data in a common microcomputer. The VaguSoft software (MediFit Diagnostics) simultaneously recorded ECG, heart rate, car-
diac vagal tone, systolic, mean, and diastolic blood pressure, blood gases, and cardiac sensitivity to the spontaneous arterial baroreflex. The EEG was recorded on a 16 channel PL-EEG in the United Kingdom (Walter Graphtek UK, West Sussex, UK) and on an eight channel paper machine (Nihon Ohden, Tokyo Japan) in Sweden. Breath by breath analyses of 47 cases excluded all interruptions.

Baseline functions are defined as autonomic activity during normal breathing with normal levels of blood gases. Control subjects voluntarily hyperventilated and held their breath in accordance with our demonstrations.

**STATISTICS**

Values are given as mean (SEM). Statistical differences were assessed using analysis of variance (ANOVA) with a two sided Student t test for probability (p) values, using Minitab for Windows 11.21.

**Results**

**BREATHING RHYTHMS**

As previously observed, no control subject showed spontaneous breathing dysrhythmias. All Rett subjects had some normal rhythm while awake but also showed 5–11 (mean 8) types of abnormal rhythm (figs 1 to 6). Valsalva breathing occurred in 26 of the 47 subjects tested (59%), Biot’s breathing in two, and Cheyne-Stokes respiration in 12 subjects with inadequate breathing.

Breathing patterns changed with age (fig 7 and table 1). Most forceful and apneustic breathers were under 5 years old and most normal and Valsalva type breathers were older. Combined percentages of breathing dysrhythmias in the 0–9 year age groups (table 1) were higher than in the older age groups (p < 0.005). The percentage of Valsalva breathing in the over 19 year age group was higher than in the youngest group (p < 0.01) or in the 6–9 year old group (p < 0.05). Inadequate breathing was most common under 18 years of age, where Cheyne-Stokes breathing was also seen. Repeat examination of six Rett subjects studied in 1987 indicated the same pattern of change with age.

**VENTILATORY EFFICIENCY IN RETT DISORDER**

Blood gases were recorded transcutaneously in 27 subjects. Carbon dioxide fell during intense hyperventilation and rose during inadequate breathing as oxygen levels fell. Mean lowest and highest PCO₂ values were 4.12 and 5.43 kPa (31 and 41 mm Hg), respectively; in two of 27 feeble breathers (7%) PCO₂ exceeded 7.98 kPa (60 mm Hg). Repeated central apnoea or Valsalva breathing was always associated with a PO₂ below 10.64 kPa (80 mm Hg). Valsalva breathers did not have raised P CO₂, while oxygen fell below 6.65 kPa (50 mm Hg) in 14 of 27 Rett subjects (52%).

**BASELINE AUTONOMIC FUNCTION**

Baseline brain stem autonomic function was analysed in 48 girls aged 2 to 35 years, mean 13.2 years, and in 11 controls aged 5 to 28, mean 10.2 (fig 8). There was no significant difference in mean resting heart rate (mean (SEM): Rett 101 (3.6) beats/min; control 92 (2.5) beats/min) or mean arterial blood pressure (Rett 79 (5.3) mm Hg; control 86 (7.1) mm Hg). Mean cardiac sensitivity to baroreflex was lower in Rett cases than in controls (Rett 3.4 (0.4) ms/mm Hg; control 6.2 (0.9) ms/mm Hg; p < 0.01). Mean cardiac vagal tone was also low in Rett cases: Rett 4.5 (0.4) units;
controls 9.2 (1.2) units in the linear vagal scale; p < 0.002).

VACANT SPELLS AND ASSOCIATED EVENTS
Epileptiform EEG features increased in sleep and diminished on alerting. Monorhythmic theta waves increased with age. Epileptiform discharges were rarely associated with clinical seizures or vacant spells. Valsalva breathing was sometimes accompanied by 4–5 Hz theta wave activity, and prolonged apnoeas caused EEG flattening. Many vacant spells in 48 of 56 subjects were associated with involuntary movements and dystonic postures and appeared during shallow breathing, long breath holds, central apnoeas, apneusis, and Valsalva breathing.

EFFECTS OF BREATHING DYSRHYTHMIAS ON AUTONOMIC FUNCTION
Voluntary hyperventilation was accompanied by increased mean blood pressure, promptly countered by increased cardiac vagal tone with a consequent decrease in heart rate to control the blood pressure, after which heart rate was restored to normal (fig 9). Vagal tone remained increased during hyperventilation and was withdrawn when hyperventilation ceased. During spontaneous hyperventilation in Rett subjects (fig 9), cardiac vagal tone increased transiently but was withdrawn and reinstated only after the hyperventilation ended. The increase in the mean blood pressure started by the onset of hyperventilation was thus uncontrolled.

Both cardiac vagal tone and cardiac sensitivity to baroreflex reflecting parasympathetic control were withdrawn at the beginning of the voluntary breath hold in control subjects and restored immediately at the end. The cardiovascular system was therefore under the sole influence of the sympathetic system at that time (fig 10).

In the Rett cases, breath holding caused prompt withdrawal of cardiac vagal tone and cardiac sensitivity to baroreflex, as in the controls, but the increase in sympathetic activity at the beginning of breath holding caused “ringing” (oscillation) of blood pressure, indicating the poor negative feedback regulation (fig 10).

RISK FACTORS IDENTIFIED IN RETT DISORDER
Five Rett subjects developed a progressive decrease in blood pressure with diminishing cardiac vagal tone and cardiac sensitivity to baroreflex. Mean arterial blood pressure approached 40 mm Hg, the level associated with spinal transection; cardiac sensitivity to baroreflex and cardiac vagal tone came close to
zero, and heart rate approached the intrinsic rate of the sinoatrial node, suggesting lower brain stem shutdown (fig 11). The EEG showed very low voltage or flat recordings, and transcutaneous oxygen levels fell. These episodes followed repeated or prolonged periods of Valsalva manoeuvres, hyperventilation, or poor ventilation. The longest such shutdown lasted three minutes.

A background of feeble breathing with low Po2 and raised PCO2 can lead to repeated episodes of exaggerated simultaneous increases in cardiac sensitivity to baroreflex, cardiac vagal tone, and blood pressure (fig 12). The term “brain stem storm” is appropriate for this event, as the functional indices of the whole brain stem—rostral, caudal, and dorsal—were simultaneously and momentarily increased. Such sudden large increases in vagal tone with poor ventilation, raised carbon dioxide, and hypoxia carry a risk of cardiac arrest.

We observed episodes of brain stem activity which did not conform to the expected physiological activation of the neurones involved. Normally, output from autonomic neurones is continuously adjusted through reflexes or pacemaker neurones according to body needs. The term “brain stem epilepsy” seems appropriate for the brief, widespread, aberrant activation of the brain stem neurones (fig 13), although no epileptiform activity was recorded at the cortex. This differed from brain stem storm in that the known physiological predisposition to increased brain stem excitability—such as feeble breathing, low Po2, and high PCO2—observed in brain stem storm were not present. Epileptic involvement of the respiratory neurones may be an additional hazard in Rett disorder.

Discussion
PHYSIOLOGICAL BASIS OF THE AUTONOMIC MEASUREMENTS
The principles underlying neuronal control of cardiorespiratory function are well documented and our methods are discussed fully in earlier reports. However, we offer a brief physiological explanation here, with comments on our results.

Sympathetic activity is closely related to mean arterial blood pressure and can thus be monitored indirectly by measuring blood pressure. In humans, the brain stem controls blood pressure directly through the common vasomotor pathway in the spinal cord. Bilateral transection of the common vasomotor pathway

Figure 5 Valsalva breathing style. Valsalva manoeuvres: breath holds or protracted inspiration capable of raising intrathoracic pressure sufficiently in magnitude and duration to reduce venous return and cause characteristic blood pressure (BP) or heart rate (HR) changes (saw toothed responses with rebounds). CVT, cardiac vagal tone; LVS, linear vagal scale. Amplitude measured in arbitrary units.

Figure 6 Less frequent breathing rhythms. Top: Cheyne–Stokes breathing—periodic breathing interrupted by central apnoea during which the breathing movements increase gradually in amplitude and decay again into apnoea. Bottom: Biot’s breathing—abrupt apnoea followed by equally abrupt regular breathing in which both the apnoea and the regular breathing have variable durations. Amplitude measured in arbitrary units.
abolishes blood pressure control, and the mean arterial blood pressure collapses to 40 mm Hg. Normal mean baseline arterial blood pressure in Rett disorder indicates normal sympathetic function in the brain stem.

Excitation of the baroreceptor, combined with the rise in arterial pressure caused by ejection of blood from the left ventricle, inhibits the sinoatrial node, delaying the onset of the following cardiac cycle, as reflected in the R-R interval. As blood is ejected into the arteries at every cardiac cycle, thus stimulating the baroreceptors, there are rapid and quantifiable pulse synchronised changes in R-R intervals. These are measured continuously by the NeuroScope™. Baroreceptor signals are the main source of excitation for the cardiovascular motor neurones in the medulla. Being the only inhibitory output of the cardiorespiratory integrative system, cardiac vagal tone is very important in rapid cardiovascular responses and is a major contributor to integrative inhibition in the system. The normal mean value for cardiac vagal tone in young supine adults breathing quietly is 10 arbitrary units in the linear vagal scale, falling to zero at full atropinisation. The cardiac vagal tone is a more direct indicator of central cardiovascular parasympathetic output than the surrogate index respiratory sinus arrhythmia. The cardiac sensitivity to baroreflex is the increase in pulse intervals per unit change in systolic blood pressure. It is calculated by quantifying cardiac

<p>| Table 1 Respiratory and autonomic results according to age group |
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<table>
<thead>
<tr>
<th>Age group</th>
<th>Mean age (years)</th>
<th>No in group</th>
<th>CVT (ms/mm Hg)</th>
<th>Normal breathing (%)</th>
<th>Inadequate breathing (%)</th>
<th>Forced breathing (%)</th>
<th>Apneustic breathing (%)</th>
<th>Valsalva breathing (%)</th>
<th>Tone type</th>
<th>Reported epilepsy</th>
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<td>7</td>
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<td>2.4 (0.5)</td>
<td>26.7 (7.7)</td>
<td>9.6 (4.7)</td>
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Values are mean (SEM).  
1Number in group = 14.  
2Number in group = 10.  
Breathing rhythm: mean (SEM) per cent of monitored time spent in each rhythm.  
Tone type: Number of subjects with hypo(tonia), normal tone, hyper(tonia), and dys(tonia) given.  
Reported epilepsy: Number in group with reports of epilepsy  
Pre/now walking solo: Number of subjects who had walked pre-regression/number of subjects who walked unaided at time of investigation.  
CSB, mean sensitivity to baroreflex; CVT, mean cardiac vagal tone.
responses to ejection pressures in each cardiac cycle as $\Delta RR/\Delta SBP$, where $\Delta RR$ is the difference between present and previous ECG R-R intervals and $\Delta SBP$ is the difference between the systolic blood pressure values in two preceding cardiac cycles. The cardiac sensitivity to baroreflex indicates the overall gain in the negative feedback in the baroreflex system set up in the nucleus tractus solitarius. Consistently low baseline cardiac vagal tone and cardiac sensitivity to baroreflex in Rett cases indicates reduced integrative inhibitions in both the nucleus tractus solitarius and the nucleus ambiguus.

During the normal initiation of an end of inspiration breath hold, the lungs fill with air and stimulate the slow-adapting pulmonary stretch receptors, leading to reduction in cardiac vagal tone and cardiac sensitivity to baroreflex. This explains the withdrawal of cardiac vagal tone and cardiac sensitivity to baroreflex at the onset of the normal breath hold. The central inspiratory drive at the beginning of the breath hold increases sympathetic tone and further decreases cardiac vagal tone and cardiac sensitivity to baroreflex. As long as the lungs are inflated, the sympathetic system remains in full control of the cardiovascular system, with minimal parasympathetic activity. Our results show that healthy people can cope with the reduced negative feedback in the parasympathetic system during a breath hold, whereas this manoeuvre is precarious in Rett disorder.

**BRAIN STEM FEATURES OF RETT DISORDER**

We have shown that the baseline brain stem functions (breathing rhythm, cardiac sensitivity to baroreflex, and cardiac vagal tone, which are maintained by complex integrative inhibitions) are affected in the Rett disorder, while baseline sympathetic tone, maintained by pacemaker activity, is preserved. Moreover, sympathetic responses during hyperventilation are poorly regulated in Rett disorder, indicating insufficient reciprocal innervation and lack of integrative inhibition within the cardiorespiratory neurones. The oscillation of blood pressure during breath holding in Rett disorder indicates lack of parasympathetic restraint of the sympathetic system because the cardiovascular system is restrained through a parasympathetic negative feedback system. That Rett subjects did maintain normal breathing while asleep may reflect improved inhibitory integration in
Breathing dysfunction in Rett disorder during sleep. The breathing dysrhythmias while awake may suggest poor integration at higher centres like the hypothalamus and the limbic cortex, where “wakefulness drive” of breathing is significantly modulated.\textsuperscript{28} Apneusis (protracted inspiration) commonly seen in the youngest Rett girls suggests a serotonin (5-HT) defect in the brain stem, as the termination of inspiration to allow initiation of expiration in humans depends in part on 5-HT\textsubscript{1A} receptors.\textsuperscript{29} Valsalva breathing was seen in older Rett survivors, the severely affected having died in adolescence. Valsalva breathing can achieve adequate CO\textsubscript{2} expulsion against inappropriate contraction of the glottis, but also contributes to aerophagy.\textsuperscript{11} Inadequate ventilation is often overlooked but it indicates weak central respiratory drive with reduced inhibition of cardiac vagal tone, rise in PCO\textsubscript{2}, and fall in PO\textsubscript{2}. The combination of hypercapnia and hypoxia optimally stimulates the peripheral chemoreceptors and, combined with weak central respiratory drive, leads to maximal cardiovagal excitation such as was seen in brain stem storm (fig 12). Brain stem shutdown may be due to postactivation or postictal neuronal quiescence after severe brain stem activation caused by forceful breathing (fig 11). Brain stem epilepsy (fig 13) is not unique to Rett cases, and we have observed it during routine autonomic examination in elderly people with syncope and in other patients with epilepsy.

Figure 10  Effects of breath holding on sympathovagal balance and baroreflex function in a Rett case and a control. The periods of breath holds are enclosed by broken vertical lines. Note the normal smooth withdrawal of cardiac vagal tone and which leaves the cardiovascular control to the sympathetic system. In the Rett case, this manoeuvre unmasked the inadequate restraint of the sympathetic system, indicated by oscillation of blood pressure and exaggerated changes in heart rate. BP, mean arterial blood pressure representing sympathetic activity; CVT, cardiac vagal tone (measured in linear vagal scale (LVS)); HR, heart rate.

Figure 11  Brain stem shutdown in a girl of 11 years. The vertical broken line marks the beginning of the autonomic shutdown (see text). BP, mean arterial blood pressure representing sympathetic activity; CVT, cardiac vagal tone (measured in linear vagal scale (LVS)); HR, heart rate; PO\textsubscript{2} and PCO\textsubscript{2}, transcutaneous partial pressure of oxygen and carbon dioxide.
POTENTIAL CLINICAL INTERVENTIONS IN RETT DISORDER

On the basis of our results, the brain stem neurotransmitters may offer a means of clinical intervention. L-glutamate is required for baroreceptor input. Serotonin receptor type 5-HT4, angiotensin-II, and enkephalin are all modulators of cardiac sensitivity to baroreflex at the nucleus tractus solitarius. 30 31 ß-Aminobutyric acid (GABA) is used to modulate cardiac sensitivity to baroreflex and cardiac vagal tone by supramedullary centres and vagal afferents from the lungs. 24 The muscarinic cholinergic system modulates cardiac vagal tone and baroreflexes. 25 32 Second messengers such as cAMP and diacyl glycerols, necessary for nerve signal transduction, may become depleted in brain stem neurones, leading to central apnoea (Harkness RA, personal communication, and ). Clinical manipulation of these factors by either supplementation or pharmacological means may be beneficial in Rett disorder.

CONCLUSIONS

Compelling clinical, neurophysiological, and neuropathological evidence points to a prenatal brain defect with early brain stem involvement in Rett disorder. 10 35 36 The labile breathing rhythms, the reduction in baseline cardiac vagal tone and cardiac sensitivity to baroreflex comparable to that of neonates, 37 and signs of the inability to restrain sympathetic responses in Rett disorder indicate brain stem immaturity and a lack of integrative inhibition, with consequent failure to respond normally to physiological demands. This explains many vacant spells and some sudden deaths. 38 39 Rett disorder is a congenital dysautonomia. The slow development, regression, and limited growth seen in Rett disorder closely match the concepts of the MECP2 gene failing to regulate target genes involved in development, thereby initiating a cascade of problems. Genes controlling brain stem neurotransmitters offer potential for clinical interventions and insight into this disorder. Our methods have proved helpful in studying the Rett disorder and will assist in the diagnosis of other conditions and in monitoring clinical interventions.
Breathing dysfunction in Rett disorder


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