Management of a severe forceful breather with Rett Syndrome using carbogen

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Abstract

We have used a novel neurophysiological technique in the NeuroScope system in combination with conventional electroencephalography (EEG) to monitor both brainstem and cortical activity simultaneously in real-time in a girl with Rett syndrome. The presenting clinical features in our patient were severe sleep disturbances, irregular breathing in the awake state dominated by Valsalva’s type of breathing followed by tachypnoea and very frequent attacks of seizures and vacant spells. Our novel neurophysiological data showed that the patient was a Forceful Breather according to the breathing categories in Rett syndrome. She had frequent abnormal spontaneous brainstem activation (ASBA) preceded by severe attacks of hypocapnoea, which was caused by a combination of Valsalva’s type of breathing and tachypnoea and all these together were responsible for the seizures and non-epileptic vacant spells. The ASBA was not detectable in conventional EEG and there were no epileptiform changes in the EEG during the seizures and vacant spells caused by the hypocapnic attacks, therefore these were pseudo-seizures. The record of brainstem activity confirmed that these were autonomic events, a kind of “brainstem epilepsy”. We successfully treated the sleep disturbance with Pipamperone, a 5-hydroxytryptophan antagonist of receptor type 2 and we prevented the severe hypocapnoea during Valsalva’s type of breathing and during tachypnoea using carbogen (a mixture of 5% carbon dioxide and 95% oxygen), which we gave by inhalation. Our treatment drastically reduced the autonomic events, promoted whole night sleep and significantly improved the quality of life in our patient. She can now participate in normal family activity which was previously impossible before treatment.

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1. Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder with six cardinal features. There are two cortical features: severe mental retardation and epilepsy [1]. The third feature is extrapyramidal or basal ganglia dysfunction indicated by: dystonia, orthopaedic deformation, muscle wasting, incoordination of thoughts and movements [1]. The most pronounced and often live-threatening are the forth and fifth features both due to brainstem dysfunction. The forth feature is likely to be due to monoaminergic dysfunction in the brainstem and
consists of dysphasia, sleep disturbance with frequent daytime sleeping and night awakening and agitation [2]. The fifth feature is likely to be due to incompetence of network inhibitions in the brainstem and is indicated by the abnormal breathing rhythms in the awake-state [3]. It is present in almost all patients with RTT. The abnormal breathing rhythms and the accompanying autonomic dysfunction may explain the sudden deaths accounting for at least 25% of all deaths in RTT [4, 5].

Irregular breathing in RTT as a consequence of immature brainstem function has been explicitly described [6]. The 13 abnormal breathing patterns were divided into three distinct categories of Feeble, Forceful and Apneustic types of breathings [7]. New insights and definitions, like ASBA (abnormal spontaneous brainstem activation), “brainstem epilepsy” and “brainstem storm”, describe the neurophysiology of these brainstem events [6]. The sixth and last feature of RTT is dysautonomia, which is now recognised as part of the brainstem features in RTT [6, 7]. In addition to delayed nociception and cold and blue extremities comes the newly described sympato-vagal imbalance in which the sympathetic tone is normal but the parasympathetic tone is very low, nearly at the neonatal level [8]. This unique imbalance gives the misleading clinical impression of a sympathetic hyperactivity in RTT. There is also a lack of integrative inhibition that prevents appropriate cardiovascular regulations during abnormal breathing with increased risks of adverse cardiorespiratory events that may be fatal [4, 6].

RTT almost exclusively affects girls between the age of 6 and 18 months [1, 9]. Recurrent as well as complex mutations and gross rearrangements are found in the gene encoding for the methyl-CpG-binding protein-2 [10–12]. This protein is ubiquitously present in the body but especially abundant in the developing brain [13]. It is involved in the methylation of DNA and in the transcription–repression in order to express yet unknown target genes while silencing others that are not required at that time [14]. It must be emphasised that not all girls with the clinical diagnosis of Rett syndrome have mutations of the MECP2 gene [15–17].

2. Case history

A girl born in 1990 was diagnosed as classical RTT by the age of 2 years. She presented with the typical history of stagnation and regression with the subsequent appearance of characteristic manifestations of RTT as previously described [18]. Recent DNA analysis identified the common R306C missense mutation in the transcription–repression domain of the MECP2 gene. Our patient started having generalized tonic-clonic seizures that were resistant to multiple anti-epileptic drug regimes in the year 1997. She started to hyperventilate at a pre-school age, in association with irregular breathing, as soon as she was awake. When she was 9 years old, she visited the Swedish National Rett Centre in Frösön where her major problems were found to be repetitive non-epileptic vacant spells with frequent Valsalva’s manoeuvres, shallow breathings and apnoea with cyanosis during the day. These respiratory abnormalities also occurred during the night causing abnormal and variable duration of night sleep. The episodes of breathing abnormalities were very distressing and life-threatening to the child. Constant supervision from her parents or carers was required for two years preceding our investigation and treatment. The vacant spells started with tachypnoea. Then she would perform Valsalva’s manoeuvres usually with her head turned first to the left and changing over later to the right. Typical sequences of events were wringing of hands, gazing upwards, stretching out with large extension movements beginning in the legs. Subsequently she becomes rigid and starts to display jerky movements of upper and lower limbs. The head and arms are then raised and thrown backwards more or less in an opisthotonus posture. Her staring eyes remain opened as if in a “panic”. Following such an “attack”, she usually becomes quiet and sleepy as if in a postictal quiescence. The episodes may be of short duration or proceed to intensive tonic-clonic seizures lasting 20–30 min. After a severe spell she becomes unconscious, often with cyanotic lips, and it is impossible to wake her up for several hours. Such episodes can happen several times during the day, but less frequently at night. By defining these episodes as “breathing attacks”, the parents are emphasising that the phenomena are different from her epileptic seizures. The vacant spells started with tachypnoea. Then she would perform Valsalva’s manoeuvres usually with her head turned first to the left and changing over later to the right. Typical sequences of events were wringing of hands, gazing upwards, stretching out with large extension movements beginning in the legs. Subsequently she becomes rigid and starts to display jerky movements of upper and lower limbs. The head and arms are then raised and thrown backwards more or less in an opisthotonus posture. Her staring eyes remain opened as if in a “panic”. Following such an “attack”, she usually becomes quiet and sleepy as if in a postictal quiescence. The episodes may be of short duration or proceed to intensive tonic-clonic seizures lasting 20–30 min. After a severe spell she becomes unconscious, often with cyanotic lips, and it is impossible to wake her up for several hours. Such episodes can happen several times during the day, but less frequently at night. By defining these episodes as “breathing attacks”, the parents are emphasising that the phenomena are different from her epileptic seizures. At the age of 11 years the patient’s anti-epileptic drug therapy was reduced to sodium-valproate monotherapy. Then Pipamperone, a 5-hydroxytryptophan antagonist of receptor type 2, was added in two daily doses of 8 mg with a 12 h interval. The main function of Pipamperone is to regulate the night sleep circadian rhythm. One year later, in September 2002, overwhelming breathing irregularities re-occurred and she was referred back to the Swedish Rett Centre in Frösön in Sweden for assessment of her brainstem function during these severe attacks.

3. Non-invasive monitoring of brainstem autonomic activity

Non-invasive monitoring of brainstem autonomic activity in RTT has been described in detail previously [6]. Briefly, the subject sat comfortably with her parents for one hour of continuous monitoring of multiple brainstem functions. The NeuroScope™ system (MediFit Diagnostics Ltd., London, UK) was used to record the following data. Heart rate (HR)
and electrocardiographic R–R intervals were recorded continuously in real-time. A stretch-sensitive resistance plethysmograph placed at the level of the xiphisternum, 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 (Finapres® Ohmeda, USA) recorded digital arterial blood pressure (BP) waveforms live continuously in real-time. A calibrated analogue output of the blood pressure waveform was fed from the Finapres to the Neuroscope™ system. Systolic (SBP), diastolic (DBP) and mean (MAP) were calculated using VaguSoft software (Medifit Instruments, London, UK). The MAP was calculated as the true arithmetic mean of pressures throughout one cardiac cycle. Blood pressure regulation indicates brainstem activity because the level of MAP in mmHg is related to neuronal activity in the rostral ventrolateral medulla oblongata [19] and bilateral transection of specific vasomotor tracts in the spinal cord that originate from the rostral medulla abolishes blood pressure regulation in humans [20].

The non-invasive index of cardiac vagal tone (CVT), which is an indicator of cardiac parasympathetic activity, was also measured on a continuous beat-to-beat basis using the Neuroscope™ system as previously described [21]. The CVT was measured in arbitrary units of a Linear Vagal Scale (LVS) as previously described [22]. The least value in this scale is zero, equivalent to full atropinization in all human subjects [22] while 10 units in the scale represents normal cardiac parasympathetic activity in young adult males lying supine in a resting state and breathing normal tidal volumes. Cardiac vagal tone is regulated in the brainstem by yet unknown nuclei in humans, of which nucleus ambiguous probably has a vital role. The non-invasive index of cardiac sensitivity to baroreflex (CSB) was measured continuously using the Neuroscope™ system as previously described [23,6]. This index is defined as “the increase in pulse interval per unit increase in systolic pressure” and its unit of measurement is ms/mmHg. The least value of CSB in this method is zero, which means that there is no beat-to-beat negative feedback regulation of the blood pressure. It is reported that this sensitivity is regulated at the level of the nucleus of tractus solitarius in the brainstem [24]. All the data recorded by the NeuroScope™ system can be viewed in real-time during the monitoring session or stored for further analyses. Video EEG (Nervus EEG, Cephalon, Denmark) was recorded in synchrony with the physiological data from the NeuroScope™ system, all of which are time-stamped for later analyses of the sequences of events. Three monitoring sessions were carried out. Two while the patient was on Pipamperone treatment (investigations I and II) and one 32 hours after withdrawal of Pipamperone (investigation III).

4. Treatment with carbogen

In order to test our hypothesis that hyperventilation with respiratory alkalosis was indeed the most important factor in the origin of the hypocapnic attacks, the patient was admitted to the paediatric intensive care of our hospital. A carbon dioxide/oxygen gas mixture (40% CO₂ and 60% O₂) at 2 liters/min was given continuously during the day by means of nasal prongs. The content of the gas mixture was chosen to result in an estimated inspired CO₂ concentration of approximately 3-4% in order to prevent hypopcapnoea and respiratory alkalosis during hyperventilation. Before this treatment was started, baseline values of heart rate, respiratory rate, transcutaneous pCO₂, pulse oximetry and frequent arterial blood gases, by means of an indwelling arterial catheter, were recorded for 48 hours. Since we had noted that during breathing attacks the patient preferentially breathed through her mouth, we taught the parents to administer a mixture of 3% CO₂ and 95% O₂ (Carbogen), which we intended to discharge the patient on, by facemask at the beginning of autonomic events in addition to the continuous diurnal administration by the nasal prongs. After the parents had been instructed how to use the CO₂/O₂ mixture in the home situation the patient was discharged. After 17 months of CO₂ therapy, the breathing problems were re-evaluated during a five-day observation period in our paediatric intensive care unit where the same vital parameters were monitored. Baseline values were obtained with CO₂ therapy and were comparable to those at the end of the first admission. Next, the CO₂ therapy was stopped for 24 hours, but was re-started when even more severe symptoms re-occurred.

5. Results

5.1. Baseline brainstem function

The indices of brainstem parasympathetic functions CVT and CSB were both very low compared to reference values for normal children of same age. Blood pressures were within normal limits and the increased resting heart rate of 92–99 is often seen in RTT and is due to decreased CVT. Extended periods of normal breathing allowed us to measure the baseline breathing rate which was 16–28 breaths/min in the three monitoring sessions (Table 1). During periods of normal breathing, the pO₂ was within the normal range (at >60 mmHg) but pCO₂ was always below the lower normal limit of 25 mmHg. Table 1 shows the mean baseline values of the cardiorespiratory variables in the three investigations.
5.2. Brainstem function during hypocapnic attack

When the patient was not breathing normally, five different abnormal breathing patterns were observed: Valsalva’s manoeuvres, tachypnoea, shallow breathing, apnoea (the longest duration was 67 s), and rapid shallow breathing. The most prominent breathing abnormalities were tachypnoea and Valsalva’s manoeuvres. During Valsalva’s manoeuvre and shallow breathing, the patient breathed normally at a rate below 35 breaths/min without any epileptiform activity in the electroencephalogram. CVT, cardiac vagal tone measured in arbitrary units of a Linear Vagal Scale; CSB, cardiac sensitivity to baroreflex measured in ms/mmHg; SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg; MAP, mean arterial blood pressure in mmHg; HR, Heart rate (beats/min); $pO_2$, partial pressure of oxygen in the blood in mmHg and $pCO_2$/partial pressure of carbon dioxide in the blood in mmHg.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>(I)</th>
<th>(II)</th>
<th>(III)</th>
<th>Reference values</th>
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<td>CTV</td>
<td>2.0</td>
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<td>4.3</td>
<td>5–10</td>
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<td>2.7</td>
<td>2.2</td>
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<tr>
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<td>135</td>
<td>120–150</td>
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<td>72</td>
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<td>60–90</td>
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<tr>
<td>MAP</td>
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<td>91</td>
<td>93</td>
<td>80–110</td>
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<tr>
<td>HR</td>
<td>99</td>
<td>92</td>
<td>96</td>
<td>65–80</td>
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<tr>
<td>$pO_2$</td>
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<td>64</td>
<td>87.3</td>
<td>&gt;60</td>
</tr>
<tr>
<td>$pCO_2$</td>
<td>–</td>
<td>23</td>
<td>19.4</td>
<td>25–40</td>
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Session (I) was recorded during a bad episode of cardiorespiratory disturbance and blood gases were not monitored. Session (II) was recorded during a relative calm in the cardiorespiratory state and Session (III) was also recorded during a relative calm, but 32 h after withdrawal of Pipamperone. Baseline state is when the patient is awake and breathing normally at a rate below 35 breaths/min without any epileptiform activity in the electroencephalogram. CVT, cardiac vagal tone measured in arbitrary units of a Linear Vagal Scale; CSB, cardiac sensitivity to baroreflex measured in ms/mmHg; SBP, systolic blood pressure in mmHg; MAP, mean arterial blood pressure in mmHg; HR, Heart rate (beats/min); $pO_2$, partial pressure of oxygen in the blood in mmHg and $pCO_2$/partial pressure of carbon dioxide in the blood in mmHg.

5.3. Treatment with pipamperone

With the monotherapy regime of anti-epileptic drug and pipamperone, the patient fell asleep easily and slept the whole night without crying spells or abnormal breathings and without the previously disturbing early awakening she used to experience. During the day, there was a remarkable reduction in the frequency of her Valsalva’s manoeuvres (Fig. 1A) and the associated secondary events that used to follow this type of breathing. This clinical improvement has persisted ever since the introduction of this treatment regime.

5.4. Withdrawal of pipamperone

During the third monitoring session (32 h after withdrawal of pipamperone) the patient was more alert, but the Valsalva’s manoeuvres were more frequent (Fig. 1B) and the $pCO_2$ went even further down (15 mmHg) due to the frequent Valsalva’s manoeuvres.

5.5. Treatment with carbogen

After $CO_2$-therapy was started, no differences in $pCO_2$ values were observed during normal breathing compared to the baseline values, while during hyperventilation, severe hypocapnoea and respiratory alkalosis could be prevented ($pH < 7.6$ and $pCO_2 > 22$ mmHg were achievable). More importantly was a striking reduction in the frequency and severity of the “hypocapnic attacks” and the ASBA that we observed during our five-day observation. In the next months, keeping the patient on $CO_2$ inhalation therapy we observed a 50% reduction in her life-threatening autonomic events compared with the previous years, this time some of the event free periods lasted more than a week. This contributed to the reduction in the number of these life-threatening events. The patient slept well without apnoea or frequent awakening and could again participate in daily activities at the day-care centre and at home.

5.6. Withdrawal of carbogen treatment for 24 h

A dramatic recurrence of breathing attacks was observed during the waking state leading to prolonged intervals in which the patient lost consciousness. These events seemed again to be triggered by severe hypocapnoea and respiratory alkalosis. Electrocardiogram and echocardiogram both gave no evidence of either pulmonary hypertension or cor pulmonale. The Q-Tc
Fig. 1. (A/B) Two segments of equal lengths of 33 min. Each showing continuous records of breathing movements during sessions (I) in A and (III) in B; both are drawn in the same scale of amplitudes. The amplitudes are shown in an arbitrary display scale of computer screen and the time was measured from the beginning of the respective monitoring session (see text for description of sessions (I) and (III)). The amplitudes of the abnormal breathing movements are so large that normal breathing appears insignificant in the illustration. Of the abnormal breathing movements, the clearly visible ones are: \(T\) = a period of tachypnoea and \(V\) = a period of Valsalva’s manoeuvre. In (A) note the relative reduction in both frequency and amplitudes of abnormal breathing movements with only a brief attack of sustained, abnormal breathing between 847 AM-1575 s. N1 = a period of normal breathing during which there were gradual inflations over several breaths and rapid deflations. N2 and N3 are periods of normal breathing, but with sustained and gradual deflations over several breaths (inspirations > expirations). N4 = a period of normal breathing with a rapid deflation at the end. N5 = a period of normal breathing with a rapid inflation at the end. N6 = a period of normal breathing sustained at a relatively constant functional volume of the lung, a rare occurrence in this patient. In (B) Note the relatively large amplitudes of the abnormal breathing movements and frequent attacks of Valsalva’s manoeuvres. There was no period of normal breathing in this segment. The solid double arrow indicates a period of hypocapnoic attack during which the patient had tonic-clonic jerks and carpo-pedal spasms.
The brainstem reacted by inducing apnoea to try and breathing caused very severe hypocapnoea in this patient.

6.2. Hypocapnic attacks

A combination of tachypnoea and Valsalva’s type of breathing caused very severe hypocapnoea in this patient. The brainstem reacted by inducing apnoea to try and increase the low pCO₂, however at the cost of a severe decrease in pO₂. This seemed to cause absence attacks and the patient becomes unsteady sometimes bending forward in her wheelchair but unaware of the surroundings. There are no epileptiform changes in the EEG during these attacks, the background remains as normally seen in Rett syndrome. However, there are increases of ASBA with severe cardiovascular instability at the same time with these attacks. The ASBA spreads rostrally or caudally affecting various brainstem nuclei as described in the Results. The patient’s so-called “seizures” were in fact autonomic events that were caused by ASBA and the severe derangement of the blood gases. The muscular “tremors” seen in this patient can be explained in several ways. They can be due to the ion imbalance between calcium and sodium secondary to the low carbon dioxide, or due to low blood sugar, anxiety or excitement associated with the abnormal head and body movements, or due to hypocapnoea with tetany. There was clinical evidence of tetany indicated by carpal spasm and episthotonus position during the attacks.

6.3. Treatment with carbogen

The rationale of carbogen treatment was to raise the level of pCO₂ in the blood to a concentration that will stop the clinical symptoms. This was necessary due to the severe hypocapnoea in this patient that seems to precipitate ASBA and seizure-like muscle activity, which all together clinically looks live threatening. This justified the drastic steps we had to take to administer the carbogen. This treatment must not be taken lightly and cannot be administered for the first time without adequate monitoring facility. A confirmation of severe hypocapnoea is required at the start and once treatment has begun, there must be proper supervision through the entire treatment session. There was an obvious need for long-term carbogen treatment in our patient, therefore the parents had to be trained how to administer and supervise the treatment. This was absolutely necessary before the patient could be discharged out of the hospital. The ASBAs are a consequence of the immaturity of the brainstem in RTT, but appears to be provoked in this patient by the hypocapnoea caused by Valsalva’s type of breathing. By preventing a fall in pCO₂ using carbogen, the sequence of events as described in the results did not occur and the patient did not proceed to the full extent of losing consciousness as it usually did.

6.4. Quality of life

The symptoms in our patient were extremely distressing, especially to her immediate relatives, causing much fear and anxiety that she may not survive another spell. The patient however always regained consciousness, even after the longest periods of apnoea and cyanosis. For many years before our intervention with this carbogen treatment, the relatives always feared that the patient might not indeed survive another attack. Our intervention has now made her look happy and content and she can once again take part in the daily family life. The physiology of Valsalva’s type of breathing is that it decreases blood pressure and increases heart rate due to the increased pressure in the thorax, which prevents the
return of blood back to the heart. The sudden forceful expiration at the end of the manoeuvre causes blood to rush back into the heart. The heart rate decreases immediately and severely and the blood pressure increases too. These swings in pulses and blood pressure cause dizziness and panic and it is surely like “riding in a roller coaster” the whole day. This was drastically reduced by our treatment resulting in much improvement in the quality of life.

7. Conclusion

We described a very severe hypocapnoea associated with non-epileptic vacant spells and seizure-like muscle activity as the clinical signs of brainstem dysfunction in a girl with RTT. We confirmed through our monitoring of the cardiovascular and respiratory variables that these phenomena were based on ASBA. ASBA is the abnormal spontaneous brainstem activation usually due to neuronal immaturity in Rett syndrome. Treatment with pipamperone improved sleep, reduced agitation and decreased both the intensity and frequency of Valsalva’s type of breathing in this girl with RTT but we are not sure of the mechanism of action of this drug and this needs further investigation. Treatment with carbogen was clearly beneficial and was required at long-term in this patient with predominantly autonomic brainstem dysfunction. We did not observe any special side effects of carbogen treatment, even at long-term. To our knowledge, this patient is the first to be treated with carbogen for severe hypocapnoea in this manner. The treatment is not a practical one regarding the materials and the space required for the gas containers, but it was the only solution for this girl to improve her daily quality of life and it turned up to be harmless. We would like to stress that the suitability of this treatment depends very much on the type of abnormal breathing and its effect on the brainstem function of the particular patient. Autonomic monitoring as described here is absolutely necessary before suitability of any treatment can be considered.

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