Rett’s syndrome is a genetic neurodevelopmental disorder with brainstem immaturity that affects one in 10 000 women. The condition shows the importance of the brainstem in cardiorespiratory medicine. There is a lack of understanding of the cardiorespiratory disturbance in the disorder within the medical community, which makes management a challenge. Therefore an international group of experienced medical practitioners from various disciplines gathered in the Swedish National Rett Centre, Frösön, to collate their experience on Rett’s syndrome and provide a practical management strategy for all health-care tiers: the Frösö Declaration.

The six cardinal features of Rett’s syndrome (table) are age-dependent. Abnormalities become evident during the first or second year of life. A regression stage, characterised by an exacerbation of brainstem features, usually seems to take place in the second year. There is poor parasympathetic development, leading to a unique sympathovagal imbalance with the misleading impression of sympathetic overactivity. A lack of integrative inhibitions in the brainstem prevents appropriate cardiovascular regulation during abnormal breathing, causing an increased risk of adverse cardiorespiratory events.5,6 Brainstem disorders are the main reasons to seek urgent medical attention in Rett’s syndrome throughout life. Multiorgan involvement of in breathing-related metabolic disorders needs professional care and includes cardiologists, anaesthesiologists, respiratory physicians, endocrinologists, nutritionists, neurologists, paediatricians, and general practitioners.

Early diagnosis to avoid long-term medical uncertainty is the primary aim. A search for mutations in the MECP2 gene in infants with unexplained developmental slurring is recommended. Then the cardiorespiratory phenotype should be established at the onset of brainstem disorders, because each of the three phenotypes is unique and needs a specifically tailored management strategy.8 Establishing the cardiorespiratory phenotype requires detailed neurophysiology.8 The primary pathophysiology is a defective control mechanism of carbon dioxide exhalation that leads to respiratory alkalosis or acidosis.

Table: Six cardinal features of brain immaturity in Rett’s syndrome

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Abnormalities</th>
<th>Clinical observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>Decreased dendritic arborisation and smaller than normal brain size</td>
<td>Severe mental retardation</td>
</tr>
<tr>
<td>Cortex</td>
<td>Epilepsy</td>
<td>Seizure activities</td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td>Monoaminergic dysfunction</td>
<td>Dystonia, no coordination of motor activities, orthopaedic deformities (most common is scoliosis), and wasting of secondary muscles with contractures</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Monoaminergic dysfunction</td>
<td>Dyspraxia, agitation, and sleep disturbances (frequent daytime sleep and night awakening)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Immaturity with incompetence of inhibitory neuronal networks</td>
<td>Abnormal breathing rhythms and lack of integrative inhibitions are probable causes of sudden deaths</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Dyautonomia</td>
<td>Cold and blue extremities and neonatal level of cardiac vagal tone against normal sympathetic tone, leading to a unique sympathovagal imbalance</td>
</tr>
</tbody>
</table>

Cardiorespiratory challenges in Rett’s syndrome

two-thirds of Tibetan people have not had access to iodised salt.

Despite the overall poor coverage, the picture is not all bleak. In Tibet, there are 890 primary schools, 118 middle schools, and 1568 teaching. Of the 470 000 students attending these schools, three-quarters eat in school dining halls 5 days a week. Happily, all school dining halls in Tibet use iodised salt in accordance with a policy and schools health-promotion programme set out by the Education Bureau of Tibet in 2005. Since then, around 350 000 school children consume iodised salt at least 5 days a week, thus achieving the required intake of iodine for children.3

*Sumei Li, Haichun Wei, Qingsi Zheng
Institute of Communicable Disease Control and Prevention (SL, QZ), and National Center for Rural Water Supply Technical Guidance (HW), Chinese Center for Disease Control and Prevention, Changping, Beijing 102206, China
lisumeinttst@163.com

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to a facial mask that fits tightly onto a patient’s face. Long-term weaning from chronic respiratory alkalosis requires carbogen treatment (5% carbon dioxide in oxygen) to move the pCO₂ towards the normal value of 39–44 mm Hg. Patients with phenotype 2 are feeble breathers who usually have fixed high concentrations of pCO₂, causing chronic respiratory acidosis, due to weak respiration. Physical activity during person-to-person contact can stimulate breathing, but is short-lived. Oral theophylline is our first choice for respiratory stimulation. Continuous positive airway pressure (CPAP) can be used at night. The endpoint of treatment is to establish normal breathing rhythm at or near normal pCO₂. These patients are highly sensitive to opioids and benzodiazepines. Weaning from artificial ventilation is difficult. Patients with phenotype 3 are apneustic breathers who accumulate CO₂ because of delayed and inadequate expirations. Oral buspirone is the drug of first choice because of its effect on apneusis. Treatment endpoint and risks are otherwise similar to those in feeble breathers.

The Valsalva manoeuvre is a common complication that affects all phenotypes and causes clinical deterioration. Its powerful excitatory effects on brainstem functions ensure recognisable clinical features and might be confused with epileptic seizures; accurate diagnosis is essential, which requires monitoring the control of autonomic function in the brainstem. Agitation in Rett’s syndrome is associated with unrestrained sympathetic activity. Identification of the trigger and its avoidance is the first line of treatment, followed by the use of time-out in sensory deprivation if this fails. Drugs of choice are risperidone or pipamperone.

Nocturnal disturbances are common in Rett’s syndrome. Management includes assessment of the circadian rhythm, identification of sleep-initiation difficulties, and identification of arousals due to breathing dysrhythmias for which CPAP might be necessary. Drug treatments include melatonin to restore the circadian rhythm, pipamperone or risperidone for agitation, and tryptophan for difficulty in sleep initiation.

Epilepsy is common in people who have Rett’s syndrome. Furthermore, brainstem events might be confused with seizures. Signs of abnormal brainstem activity include blinking of the eyes, facial twitching, vacant spells with no epileptiform activity in the electroencephalogram, and hypopacnic attacks with tetany and cyanosis. Classification of these clinical events requires simultaneous monitoring of brainstem and cortical neurophysiology, and correlation with behaviour.

Reduction of clinical seizures is the main aim, but treating electroencephalographic abnormalities without any clinical correlate is rarely successful. The combination of sodium valproate and lamotrigine is especially useful. We have less experience of controlling autonomic paroxysms of the brainstem with gabapentin and pregabalin, which were used to stabilise the neuronal membrane. Stimulation of the vagus nerve has also been tried. The last two strategies—ie, pharmacological (gabapentin and pregabalin) and electrophysiological (vagal nerve stimulation)—both deserve further clinical assessment in more than one centre.

Daily energy and water requirements can be much higher than are often realised, especially in forceful breathers and Valsalva manoeuvres. Nutritional management in Rett’s syndrome should include the calculation of daily food intake and energy requirements by a dietitian. Measurements of body-mass index and skin folds are useful to monitor a patient’s progress. Comprehensive management on an individual basis has substantial effects on the health and longevity of people with this disorder and involves many specialists. In the Frösö Declaration, we are convinced that clinical treatment of Rett’s syndrome should not be based on personal anecdotal experience and declare that understanding the cardiorespiratory features is the key to providing appropriate and effective management.

*Peter O O Julu, Ingegerd Witt Engerström, Stig Hansen, Flora Apostapopoulos, Bengt Engerström, Giorgio Pini, Robert S Delamont, Eric E J Smeets

Wingate Institute of Neurogastroenterology, Queen Mary School of Medicine and Dentistry, Whitechapel, London E1 2AJ, UK (POOJ); Rett Centre, Östersund Hospital, Frösön, Sweden (IWE, BE, POOJ); Institute of Neurological Sciences, South Glasgow University Hospitals, Glasgow, UK (SH, FA); Child Neuropsychiatry and Centro Rett Versilia, Area Vasta Toscana, Nord-Occidentale, Italy (GP); Regional Neuroscience Centre, King’s College Hospital NHS Foundation Trust & King’s College London, London, UK (RSD); and Department of Clinical Genetics, University Hospital Maastricht, Maastricht, Netherlands (EEJS)

p.julu@imperial.ac.uk

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Does blood discriminate?

More than 81 million units of blood are collected globally each year, according to WHO, but only 45% is donated to developing and transitional countries despite more than 80% of the world’s population inhabiting them.1 The fourth World Blood Donor Day on June 14 draws attention to the need for donors to give blood regularly to prevent shortages, particularly in developing countries. The increasing need for donated blood, a result of medical advances that allow many more people to survive illness and injury, should perhaps prompt re-examination of those groups of people currently restricted from donating blood.

To maintain the safety of the blood supply, groups at high risk of blood-borne infections are banned from giving blood in many countries. Yet out of 133 countries that provided data, WHO found that 31 countries are still not able to screen fully for HIV, hepatitis B and C, and syphilis.1 WHO is working towards global donation on the recommendation of the Advisory Committee on the Safety of Blood, Tissues and Organs2 and also applies on the USA and many countries in Europe. In England alone, the policy affects over 490 000 men, according to 2001 figures.3 Gay-rights campaigners have denounced the ban as discriminatory4 but the Terrence Higgins Trust, the UK’s largest HIV and sexual health charity, attributes this attitude to a lack of understanding of the epidemiological data and the current capabilities for screening or treating blood for infection, which are behind the policy.

The UK National Blood Service excludes men who have sex with men from donating blood because statistics indicate that they are at higher risk of carrying sexually transmitted infections.2 Because the Service relies only on antibody-recognition tests to screen blood for some infections, there is a 3-month window during which these infections could go unrecognised. 73 000 adults are living with HIV in the UK, around of third of whom are unaware of their HIV status.5 Of an estimated 7800 people diagnosed with HIV in the UK in 2006, just over 2700 were men who have sex with men, mostly acquired in the UK, while a large proportion of the heterosexual transmissions were acquired in Africa.5

In an effort to allow men who have sex with men to donate, Australia has a deferral policy where men can begin donating 12 months after their last sexual contact with another man.6 In New Zealand men are deferred for 10 years and New Zealand Blood report no cases of transfusion-associated infection since 1985.7 The UK National Blood Service says that changing the policy to allow men who have sex with men to donate 12 months after their last sexual contact would increase the risk of HIV-infected blood entering the