Rett syndrome: Neurologic and metabolic aspects
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Citation for published version (APA):

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Respiratory disturbances in Rett syndrome:
don’t forget to evaluate upper airway obstruction

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Journal of Child Neurology 2012;27:888-892
Abstract

Rett syndrome is characterized by loss of motor and social functions, development of stereotypic hand movements, seizures and breathing disturbances. This study evaluates the presence of overnight respiratory disturbances. Polysomnography in combination with a questionnaire (the Sleep Disturbance Scale for Children) was performed in 12 Dutch patients with Rett. Respiratory disturbances were present in all, clinically relevant in 10 (apnea hypopnea per hour 1.0-14.5). In 8 children, central apneas were present during the day, often with obstructive apneas at night. In 6, obstructive sleep apnea syndrome (OSAS) was diagnosed, in 3 severe, with frequent oxygen desaturations. Significant respiratory complaints were present in 3 patients, all had obstructive sleep apnea syndrome. Of the 12 patients with Rett, 8 (67%) snored, and in 5 OSAS was present. In children, hypertrophied tonsils and adenoids are a common cause of obstructive sleep apnea syndrome (OSAS), which may benefit from therapeutic intervention. We recommend performing polysomnography in patients with Rett syndrome and respiratory complaints.

Keywords: Rett syndrome, respiratory disturbances, Obstructive Sleep Apnea Syndrome (OSAS)
Introduction

Rett syndrome is a progressive neurodevelopmental disorder and one of the most common causes of mental retardation in girls. Diagnosis is made on clinical characteristics, but in 97% of patients a dominant mutation in the MECP2 gene (which encodes for the methyl-CpG-binding protein 2) on the X-chromosome is found. MECP2 is a DNA methylation dependent transcriptional repressor. Alternative MECP2 functions are enhancement/activation of gene expression and chromatin regulation.

Typical characteristics of Rett syndrome are loss of purposeful hand skills, motor and communication dysfunction, cognitive impairment, and the development of stereotyped hand function and seizures. In addition, breathing disturbances such as hypoventilation, central apnea, episodic hyperventilation, air swallowing and Valsalva maneuvers may be present. Bradycardia predominates during sleep, while during daytime alternating tachycardia and bradycardia are present. The severity of these breathing and cardiac disturbances in a Rett girl varies significantly from day to day. Breathing disturbances in Rett girls occur mainly when the girl is awake, and can be very severe and life threatening. Recurrent breath holds might even cause prolonged QT syndrome.

Julu et al. classified patients according to daytime cardiorespiratory disturbances in three groups: 1) forceful breathers, who have a fixed low partial pressure of carbon dioxide (pCO₂); 2) feeble breathers, who have a weak respiration with chronic high pCO₂; and 3) apneustic breathers, who have long-lasting apneas and accumulate CO₂. Respiratory disturbances during sleep, such as central apnea and hypoventilation, in Rett girls have been reported only occasionally. In non Rett persons respiratory abnormalities more often occur in sleep than when awake, and consist mainly of Obstructive Sleep Apnea Syndrome (OSAS).

The aim of the present study was to evaluate the presence of overnight respiratory disturbances (such as Obstructive Sleep Apnea Syndrome) in a cohort of Rett patients.
Patients and Methods

We investigated 12 patients with Rett syndrome (mean age 8 years), including one adult patient (aged 33 years). Nine patients participated in an extended investigation for treatment of Rett syndrome, approved by the Medical Ethical Committee of the AMC Amsterdam. Two patients with Rett (patient 1 and 2) were enrolled during routine clinic visits. Rett syndrome girls of all ages, diagnosed according to the clinical criteria and preferably with an MECP2 mutation, could participate.\(^5\) In 1 patient (patient no 12) polysomnography was performed because of recurrent pneumonia and oxygen desaturations.

The Hagberg classification was used to determine clinical stage. Briefly summarized: stage I involves early developmental stagnation; stage II, regression of development and loss of motor and verbal skills, and development of stereotypic hand movements; stage III, pseudo-stationary period (time span of years or decades); and stage IV, late motor deterioration and non-ambulant Rett syndrome girls. Rett syndrome girls aged \(\leq\) 10 years and not yet able to walk are classified as stage III.\(^5\)

In addition, the modified symptom severity score (SSS) was used for more detailed severity classification. In this scale, individual clinical scores of 6 items such as onset of symptoms (maximum score 5), growth parameters (maximum 7), motor (maximum 16) and communication function (maximum 8), Rett behavior disturbances (maximum 9) and seizures (maximum 5) are summed (score range 1-50). A higher score indicates earlier onset or severity.\(^13\) The presence of epilepsy was not a contraindication for study participation.

Since we focused on respiratory disturbances at night, we used a selection of the Dutch version of a parental questionnaire, the validated Sleep Disturbance Scale for Children (SDSC), to categorize sleep and breathing disturbances.\(^14\) The questionnaire included 3 questions on breathing disorders: (1) Does the child have difficulty breathing during the night? (2) Does the child gasp for breath or is the child unable to breathe during sleep? and (3) Does the child snore? These questions were scored on a Likert-type scale, with higher values reflecting greater clinical severity: 1=never, 2=occasionally, 3=sometimes, 4=often (3-5 times a week), and 5=always. The maximum score for these 3 questions was 15: a score of \(\geq\) 7 was considered clinically relevant.\(^{14}\)
Polysomnographic recordings were performed overnight (at the Department of Pediatrics, AMC, Amsterdam) using similar conditions for all girls with Rett. Polysomnographic recording included breathing pattern recordings of respiratory effort, with an abdominal and thoracic band, and nasal airflow and pressure recording with a nasal cannula pressure transducer. The Embla Polysomnograph with Remlogic sleep analysis software was used. The following measurements were evaluated: the presence of apneas, snoring, flow limitation, oxygen saturation (SpO2), heart rate frequency, electroencephalography and pCO₂ transcutaneous (if available).

For classification of the breathing disorders the American Academy of Sleep Medicine manual for children was used.15 The apnea threshold was defined as an 80% reduction of the amplitude and breathing frequency with a duration of ≥ 10 seconds. Apneas were differentiated into central and obstructive. In central apnea there was no airflow and no abdominal-thoracic movement. Obstructive apnea was defined as no airflow despite chest wall and abdominal movements, caused by upper airway obstruction. In mixed central-obstructive apnea both phenomena were present. In the case of hypoventilation the upper airways were partly obstructed. A hypopnea was defined as a 50% reduction of breathing amplitude for at least 10 seconds. The obstructive apnea-hypopnea index (OAHI) was the total number of obstructive apneas and hypopneas per hour. An apnea-hypopnea index of ≤ 1 has been reported in healthy children.15-17 For the present study an apnea-hypopnea index of 1 to 5 was considered mild Obstructive Sleep Apnea Syndrome, apnea-hypopnea index 5 to 10 moderate Obstructive Sleep Apnea Syndrome, and an apnea-hypopnea index > 10 severe Obstructive Sleep Apnea Syndrome.17,18

Snoring is the breathing sound as a result of narrowing of the upper airways, and the presence of snoring is recorded. Flow limitation means an increased airway resistance without simultaneous obstructive apneas and hypopneas. Flow limitation is detected by a nasal cannula pressure transducer system, counting the number of flattened waves of the nasal airflow. The flow limitation index is the number of flattened waves as a percentage of the total wave count and is considered abnormal above 10%.19 Increased flow limitation index with sleep fragmentation and daytime symptoms, but with normal apnea-hypopnea index, is commonly named upper airway resistance syndrome; in the present study this is scored as mild Obstructive Sleep Apnea Syndrome.
Average oxygen saturation (SpO₂) was measured using pulse oximetry. An oxygen desaturation was defined as a > 4% decrease from the baseline SpO₂. The oxygen desaturation index is the number of these desaturations per hour. The lowest SpO₂ is shown (SpO₂ nadir). Definitions related to heart rate frequency are: bradycardia < 50 beats/min and tachycardia > 220 beats/min. Transcutaneous pCO₂ was considered to be abnormal when > 50 mmHg.

Results

Of the 12 stable patients with Rett syndrome in this study, 10 were in stage III and 2 were rated as stage IV (nonambulatory). The symptom severity scores were similar: mean score was 23 (SD: 5; range 14-29). In 83% of the group, an MECP2 mutation was present (not in patients 6 and 9). Eight of the 12 patients (67%) experienced seizures and often used multiple (range, 1-3) antiepileptic drugs. All patients with Rett had an average or below average weight for age (range -2 to 0 SD), except for patients 3, 6 and 12 (Table 1). Body height and skull circumference were mainly below average (range -2 to 0 SD).

Table 1 presents the polysomnographic results. Polysomnographic recordings were started in the afternoon until early morning, with a mean period of 705 min (11 hours and 35 minutes) (range 563-1061 minutes). All 12 patients with Rett demonstrated apneas, which were considered clinically relevant in 10 (apnea hypopnea per hour 1.0-14.5). In 8 children, central apneas were present, as previously shown only during the daytime or at night, when the patient was awake. In these 8 patients, polysomnography often revealed obstructive apnea during the night. In 6 patients (patients 1-6), the diagnosis of Obstructive Sleep Apnea Syndrome was made based on the increased apnea-hypopnea index and/or nasal flow limitation index. In 3 children Obstructive Sleep Apnea Syndrome was severe (patients 2, 3, 6 Obstructive Sleep Apnea Syndrome III). In these patients the mean SpO₂ was ≥ 92%, but the minimal SpO₂ was as low as 51% and oxygen desaturations frequently occurred. Heart rate frequency was variable and bradycardia occurred mainly at night.

Eight of the 12 patients with Rett (67%) snored, and in 5 of this group obstructive nasal air flow and/or obstructive apnea-hypopnea were present and the diagnosis of Obstructive Sleep Apnea Syndrome was made. The Sleep Disturbance Scale for Children (SDSC) scores were available for 8 patients (7 snorers) and showed
Table 1: Results of polysomnography and the Sleep Disturbance Scale for Children (SDSC)

<table>
<thead>
<tr>
<th>ID #</th>
<th>Age Years</th>
<th>Stage</th>
<th>AHI</th>
<th>OAH</th>
<th>FLI</th>
<th>Snore</th>
<th>SpO2 mean</th>
<th>SpO2 nadir</th>
<th>ODI</th>
<th>Conclusion</th>
<th>SDSC</th>
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Legend Table 1:
Stage, Hagberg clinical stage III, pseudo-stationary period; stage IV, late motor deterioration and non-ambulant
AHI, apnea hypopnea index: amount of apnea per hour (normal ≤1); OAH, obstructive apnea hypopnea index per hour
OSAS I (mild), AHI 1-5; OSAS II (moderate), AHI 5-10; OSAS III (severe), AHI > 10
FLI, flow limitation index (abnormal >10%); SpO2 mean oxygen saturation; SpO2 nadir: minimal oxygen saturation;
ODI, oxygen desaturation index (number of desaturations > 4% per hour); SDSC, respiratory questions of the validated Sleep Disturbance Scale for Children, significant score > 7; NA, not available; *second polysomnographic recording in the same patient
significant nighttime respiratory complaints in 3; polysomnographic recordings confirmed Obstructive Sleep Apnea Syndrome in all 3 patients.

Patient 2 died unexpectedly at home during the night, within 16 days after the polysomnography. No treatment for the Obstructive Sleep Apnea Syndrome had been started. This patient was known to have asthma and use daily inhalers; this was complicated by a pulmonary infection, for which an antibiotic had just been started. One non-ambulatory patient (no. 12) had a few obstructive apneas (apnea hypopnea per hour 2.4), but at the same time the mean SpO\textsubscript{2} was continuously decreased (90.1%) associated with frequent oxygen desaturation (oxygen desaturation index 22.6) as low as 70% and increased mean pCO\textsubscript{2}. This latter patient suffered from chronic hypoventilation because of pulmonary compression caused by severe scoliosis.

Patients 3 and 4 underwent an adenotonsillectomy based on the polysomnographic findings. In patient 3, repeated polysomnography demonstrated a significant decrease of apnea hypopnea per hour but, since the nasal flow limitation index was increased, the diagnosis of mild Obstructive Sleep Apnea Syndrome was made (Table 1). Patients 5 and 6 underwent (adeno)tonsillectomy prior to polysomnography and no otolaryngology treatment options were available\textsuperscript{20}, although regrowth of adenoid tissue should always be evaluated.

**Discussion**

Respiratory disturbances were present in all patients with Rett to some extent and were clinically significant in most of them. The majority of our patients experienced long-lasting apnea, often accompanied by impressive desaturations. Most apnea had a central origin during daytime. One of the first polysomnographic studies in Rett syndrome demonstrated respiratory disturbances during wakefulness.\textsuperscript{21} This was confirmed by Southall et al., who demonstrated hyperventilation in the awake state in the majority of patients with Rett syndrome, often followed by prolonged apnea that resulted in hypoxemia.\textsuperscript{22} Later on, 3 of daytime cardiorespiratory disturbances were identified: the forceful, feeble and apneustic breathers.\textsuperscript{10,11} Differentiation of these daily breathing type abnormalities is important for clinical management, since especially the feeble breathers do not tolerate opiates and benzodiazepines.\textsuperscript{10}

The pathogenic mechanism of these various respiratory disturbances is not fully understood, but might be caused by brainstem dysfunction. Studies in Rett mouse
models have demonstrated early reduced expression of γ-aminobutyric acid receptors (GABA), which may be responsible for delayed maturation of respiratory cell groups in the brainstem.\textsuperscript{23} Dysfunction of central and vagal control of post-inspiratory activity was shown in a working heart-brainstem preparation of MECP2 knock-out mice, causing breathing arrhythmias, such as repetitive apnea.\textsuperscript{24}

We focused on breathing disturbances during the night. Remarkably, in 50% of our patients with Rett syndrome, besides the central apneas, significant obstructive apneas were present, together with an increased flow limitation index, compatible with Obstructive Sleep Apnea Syndrome. The presence of these obstructive apneas was less frequent than the central apneas, but they were often accompanied by desaturation. Obstructive Sleep Apnea Syndrome causes intermittent hypoxemia, acute cardiovascular changes, sleep disruption, and neurocognitive defects.\textsuperscript{16,18} Studies in patients with Rett syndrome have shown a clear relationship between respiratory problems and sleep and behavioral disturbances.\textsuperscript{25} Furthermore, Obstructive Sleep Apnea Syndrome can aggravate seizures and treatment of Obstructive Sleep Apnea Syndrome improves seizure control in children with neurodevelopmental disorders.\textsuperscript{26,27} In our Rett population, 67% experienced seizures. Even minor upper airway infections, frequently present in our patients with Rett syndrome, can increase the number of seizures.\textsuperscript{28} Hypertrophied tonsils and adenoids are the most common cause of Obstructive Sleep Apnea Syndrome in children.\textsuperscript{27} Adenotonsillectomy reduces the amount obstructive apneas.\textsuperscript{20} In the case of Obstructive Sleep Apnea Syndrome, otolaryngology evaluation is warranted to evaluate for adenotonsillar hypertrophy. In patients with Rett, because upper airway infections, hearing disturbances\textsuperscript{29} and Obstructive Sleep Apnea Syndrome are frequently present, we emphasize the importance of otolaryngologic evaluation.

In our patients with Rett snoring was present in 68%, most of them had signs of upper airway obstruction or Obstructive Sleep Apnea Syndrome and the Sleep Disturbance Scale for Children (SDSC) often revealed sleep breathing disorders. In another population of 7-year-old normally developed children, 8.5% were habitual snorers, while 7 children (0.69%) had Obstructive Sleep Apnea Syndrome. Three years later, 65% of these habitual snorers had stopped snoring. Of the 7 Obstructive Sleep Apnea Syndrome children, 5 had persistent snoring and polysomnography revealed more severe Obstructive Sleep Apnea Syndrome in these 7 children.\textsuperscript{30} Therefore, in the case of persistent snoring and sleep breathing-related complaints, polysomnographic evaluation is recommended.
The number of Rett patients in the present study is small; however, because about 50% showed Obstructive Sleep Apnea Syndrome and may benefit from therapeutic interventions, we advise not to hesitate to perform polysomnography in patients with Rett syndrome.
References


