Rett syndrome: Neurologic and metabolic aspects

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Diagnostic use of Brainstem Auditory Evoked Potentials in Rett patients with breathing disorders?

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Abstract

Rett syndrome is a neurodevelopmental disorder characterized by motor and communication dysfunction, development of stereotypic hand function and seizures. Many patients have severe respiratory problems such as hyperventilation and apnea, caused by brainstem dysfunction. Brainstem auditory evoked potentials (BAEP) are used for evaluation of brainstem dysfunction in MS, Chiari malformations and other neurological disorders. We evaluated the diagnostic use of BAEP, in selected (unsedated) Rett patients with proven respiratory abnormalities. Nine selected, unsedated, Rett patients, genetically confirmed in 77%, participated. All had proven respiratory abnormalities, according to parental questionnaires (the Rett syndrome Motor Behavioral assessment and the Sleep Disturbance Scale) and polysomnography (PSG). The PSG demonstrated clinical relevant central apneas in six (75%). BAEP recordings showed normal brainstem conduction, despite proven respiratory abnormalities in all. In our group of Rett patients, with proven respiratory disturbances, no brainstem conduction disturbances were present. BAEP recording is not a suitable diagnostic tool in Rett patients.

Keywords: Rett syndrome, breathing disturbances, central apnea, BAEP, brainstem dysfunction, Rett syndrome Motor Behavioral assessment
Introduction

Rett syndrome is a neurodevelopmental disorder, characterized by loss of purposeful hand skills, motor and communication function, cognitive impairment, and the development of stereotypic hand function and seizures.\textsuperscript{1} A dominant mutation in the MECP2 gene, required for correct neural function, is often present. Many patients have severe respiratory problems, such as chronic hypoventilation, central apnea, episodic hyperventilation and air swallowing.\textsuperscript{2} Functional studies have demonstrated brainstem dysfunction, causing breathing dysrhythmias, heart rate and blood pressure instability and vagal tonus imbalance.\textsuperscript{2} To evaluate the functionality of the brainstem, brainstem auditory evoked potentials (BAEP) is used in various neurological disorders, like MS. In Chiari malformations breathing abnormalities and brainstem dysfunctions often occur, and BAEP is a useful predictive tool.\textsuperscript{3} We evaluated in Rett patients, with proven respiratory abnormalities suggestive of brainstem disturbances, the diagnostic use of BAEP.

Patients and Methods

This investigation was approved by the Medical Ethical Committee. Nine Rett patients, with respiratory complaints or disturbances participated (Academic Medical Center, Amsterdam). The Hagberg classification classified 7 as stage III (pseudo-stationary period), and 2 as stage IV (late motor deterioration and non-ambulant).\textsuperscript{1}

BAEP was recorded with a Nicolet Viking IV system. Rarefaction clicks of 95 dB nHL were delivered to the investigated ear by headphone, while the other ear was masked by 40 dB (Frequency 11.1 Hz). BAEPs were recorded from the vertex (Cz) electrode and using ipsilateral earlobe reference. BAEP values for girls aged ≥ 4 years consisted of peak I: 1.30-2.10, III 3.58-4.26, V 5.32-6.07. The I-V interval (representing conduction from the auditory nerve to the upper pons: normal values 3.54-4.38), I-III interval (auditory nerve to the brainstem entrance; normal value 1.91-2.51) and III-V interval (lower to the upper pons; normal value 1.44-2.08) were measured.\textsuperscript{4} No sedation was used.

Polysomnographic recordings in our Rett patients have been described previously.\textsuperscript{5} An obstructive AHI (the total amount of apnea and hypopnea per hour) of ≤ 1 is normal in healthy children. A central apnea lasting ≥ 20 seconds is considered clinically relevant. Two supplementary parental questionnaires were used. The Rett syndrome Motor Behavioral assessment, evaluates the presence of hyper-
ventilation, apnea and air-saliva expulsion/drooling using a five-point rating scale (maximum score of 12),\textsuperscript{6} score ≥ 6 clinically relevant. The validated Sleep Disturbance Scale for Children (SDSC), evaluates night-time 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?\textsuperscript{7} Maximum score 15, score of ≥ 7 clinically relevant.

**Results**

Nine stable, clinical diagnosed Rett patients participated, mean age of 8.5 (range 4-14 years), and one adult. Table 1 presents the patients’ characteristics. In 78% a MECP2 mutation was present. Seven patients (78%) experienced seizures, for which multiple antiepileptic drugs were prescribed.

Patients’ history and questionnaires revealed breathing abnormalities in all, being moderate to severe in six patients. Symptoms were snoring (55%), difficulty breathing at night (33%), apnea and gasping (67%), hyperventilation (55%) and air-saliva expulsion or drooling (67%).

Polysomnographic recordings demonstrated an increased central AHI (C-AHI 1) in six of the eight (75%) investigated patients.

Mean interpeak BAEP latencies and waves were within normal limits in all (table 2). In one patient (ID no. 2), wave I was delayed, suggestive of a peripheral ear problem.

| Table 2: BAEP mean latencies (msec) and standard deviations (sd) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Left ear                        |                 |                 |                 |                 |                 |
| I-III (sd)                      | 2.15 (0.12)     | 2.00 (0.06)     | 4.15 (0.17)     |                 |                 |
| Right ear                       |                 |                 |                 |                 |                 |
| I-III (sd)                      | 2.14 (0.20)     | 1.99 (0.11)     | 4.13 (0.25)     |                 |                 |

Normal value: I-III interval: 1.91-2.51; III-V interval: 1.44-2.08; I-V interval: 3.54-4.38
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Table 1: Clinical characteristics and results of the BAEP

<table>
<thead>
<tr>
<th>ID No.</th>
<th>Age Years</th>
<th>Clinical stage</th>
<th>Seizures (AED)</th>
<th>AHI</th>
<th>C-AHI (&gt;1)</th>
<th>RMBA (≥ 6)</th>
<th>SDSC (≥ 7)</th>
<th>BAEP</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>III</td>
<td>yes, VPA</td>
<td>3.7</td>
<td>2.7</td>
<td>6</td>
<td>5</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>III</td>
<td>yes, VPA, CLB, LEV</td>
<td>11.3</td>
<td>0.8</td>
<td>4</td>
<td>11</td>
<td>Top I delayed right side</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>III</td>
<td>yes, VPA, LTG</td>
<td>3.7</td>
<td>2.3</td>
<td>12</td>
<td>11</td>
<td>Normal</td>
</tr>
<tr>
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<td>14</td>
<td>IV</td>
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<td>11.0</td>
<td>1.0</td>
<td>7</td>
<td>13</td>
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<tr>
<td>5</td>
<td>10</td>
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<td>4.8</td>
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<tr>
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<td>III</td>
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<td>3.9</td>
<td>2.8</td>
<td>10</td>
<td>5</td>
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</tr>
<tr>
<td>7</td>
<td>14</td>
<td>IV</td>
<td>yes, TPM, CBZ, PB</td>
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<tr>
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<td>III</td>
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<td>3.1</td>
<td>2.5</td>
<td>12</td>
<td>5</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Clinical stage (Hageberg): III = pseudo-stationary period, stage IV = late motor deterioration and non-ambulant Rett patients (>10 years).
AED = anti-epileptic drugs: VPA= Valproic acid, CLB = Clobazam, LEV= Levetiracetam, LTG= Lamotrigine, TPM = Topiramate, CBZ = Carbamazepine, PB=Phenobarbital
AHI = apnea hypopnea index ; C-AHI: central apnea hypopnea index, ≥ 20 seconds clinically relevant (bold)
RMBA = Rett syndrome Motor Behavioral assessment (respiratory) score ≥ 6 clinically relevant (bold)
SDSC = Sleep Disturbance Scale for Children, total score ≥ 7 significant (bold)
BAEP: Brainstem Auditory Evoked Potentials, n.a. = not available

Discussion

All of our Rett patients had breathing abnormalities, based on the questionnaires and polysomnographic recordings. Six of these patients had documented central apneas. Despite this, BAEP evaluation showed normal brainstem interpeak latencies. Earlier studies on BAEP measurements showed conflicting results. In the nineties, in 36 clinically diagnosed Rett girls, no BAEP abnormalities were reported. However, in a recent study in 89 Rett girls, BAEP results were compared between MECP2 positive (78), MECP2 negative and sedated patients. The authors demonstrated longer I-V and III-V interpeak latency intervals in sedated MECP2 positive Rett patients, compared to non-sedated and MECP2 negative patients. In a group of Rett girls with seizures or hyperventilation wave III BAEP abnormalities were present, however sedation and phenytoin were used in some.
In our group of patients, no sedation and no phenytoin was used. Despite the small amount of patients, all showed prominent breathing disorders, highly suggestive of brainstem dysfunction, but without prolongation of BAEP interpeak latencies. Therefore, BAEP recording is not a suitable diagnostic tool to document brainstem dysfunction in Rett patient.
References


