Correlations between neurophysiological, behavioral, and cognitive function in Rett syndrome

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Correlations between neurophysiological, behavioral, and cognitive function in Rett syndrome

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ABSTRACT

Rett syndrome, a neurodevelopmental disorder affecting mainly females, is caused by a mutation of the MeCP2 gene. Girls with Rett syndrome manifest diverse behavioral and cognitive phenotypes, and the reasons for this variability remain unknown. In addition, girls with Rett syndrome often have epileptic seizures and abnormal EEGs, the characteristics of which differ with the patient. The aim of the study was to verify if neurophysiological and epileptological characteristics could be correlated with cognitive measures, obtained using eye tracker technology, and behavioral scores (Vineland Adaptive Behavior Scales and Rett Assessment Rating Scale) in 18 patients with Rett syndrome (mean age 13.7 years) at clinical stages III and IV. Age at epilepsy onset and seizure frequency were strictly correlated with neuropsychological outcome, as were EEG stage and distribution of paroxysmal abnormalities. Our findings demonstrate that neurophysiological features should be considered prognostic of cognitive and behavioral outcome in the clinical management of Rett syndrome.

1. Introduction

Rett syndrome (RS) is an X-linked dominant neurodevelopmental disorder, affecting almost exclusively females, with an incidence ranging from 1/10,000 to 1/15,000. Clinical diagnosis of the classic form relies on a battery of obligatory criteria such as normal pre-/perinatal period and normal head circumference at birth, followed by loss of acquired skills such as communication and purposeful hand use associated with onset of stereotypies. Additional characteristic features include deceleration of head growth, gait posture ataxia, breathing dysfunction, and epilepsy [1]. About 80% of females with classic RS and 25 to 75% of those with variant forms, depending on the criteria used for diagnosis and size and age of sampled population, have mutations in MeCP2 (methyl CpG binding protein2), a transcriptional repressor gene located on Xq28 [2].

Several studies have reported a relationship between some characteristics of the phenotype and the genotype, but patients with the same MeCP2 mutation can vary greatly in phenotype, so there may be other mechanisms modulating the clinical presenta-

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hand apraxia/dyspraxia, apparently preserved ambulation ability, and some communicative ability, mainly eye contact) or stage IV (late motor deterioration, with progressive loss of ambulation ability), according to the criteria for classic RS of Hagberg et al. [10]. Their demographic, developmental, clinical, behavioral, and genetic information, collected from all available sources (parent/caregiver reports of past history and current behavior and features, previous clinical reports, and direct observation and examination of the girls) were entered into a database.

Neurological examination focused on epilepsy characteristics (age at seizure onset, seizure types, course of epilepsy, and antiepileptic drugs [AEDs]).

As for MeCP2 mutations, four patients had R306C; two patients each had R270X, R294X, and R255X; four had C-terminal deletions; and the remaining four had T322A, R106W, R133C, and R168X.

Mean age at epilepsy onset was 5.1 years (range = 1–14); seizures were focal in eight patients, tonic in five, generalized tonic–clonic in three, myoclonic in one, and atonic in one. Seizures were controlled in four cases and occurred sporadically in five patients. In the other cases, epilepsy was drug resistant, and seizure frequency was described as monthly in two, weekly in six, and daily in one patient.

Eleven girls were on AED monotherapy and six on polytherapy. In one patient, therapy was discontinued because of seizure freedom.

Detailed clinical, neurophysiological, behavioral, and genetic features of the patients are listed in Table 1.

2.2. Neuropsychological assessment

Patients underwent EEG video-polygraphic recordings during wakefulness using a computerized EEG System (Micromed System Plus, Micromed s.r.l., Mogliano Veneto, TV, Italy). Scalp electrodes were positioned according to the International 10/20 system. EMG electrodes were used for deltoid muscles and/or distal muscles if tremor was present. Electrocardiograms were obtained and breathing effort was assessed. Video/EEG recording typically lasted 20–30 minutes.

The EEGs were evaluated independently by two of the authors (A.V. and F.L.) and were classified according to Glaze et al. [4] as EEG stage III (moderate to marked slowing of background activity with dominant theta and delta activity) or IV (no occipital dominant rhythm and marked slowing of background activity). Moreover, we identified four subgroups of EEG abnormalities (1) theta slow activity over the frontal and central regions (eight cases) (Fig. 1); (2) frontocentroparietal spikes (eight cases) (Fig. 2); (3) generalized spike and waves (one case) (Fig. 3); (4) diffuse subcontinuous spike and waves suggestive of epileptic encephalopathy (one case) (Fig. 4).

2.3. Behavioral measures

2.3.1. Vineland Adaptive Behavior Scales

The Vineland Adaptive Behavior Scales [11] are designed to support the diagnosis of intellectual and developmental disabilities. The Scales are organized in four domains: Communication (Receptive, Expressive, Written); Daily Living (Personal, Domestic, Community); Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills); and Motor Skills (Gross, Fine). The reliability of the Scales was established as follows: split-half, 0.73–0.93 for the Communication domain, 0.83–0.92 for Daily Living Skills, 0.78–0.94 for Socialization, 0.70–0.95 for Motor Skills, 0.84–0.98 for Adaptive Behavior Composite, 0.77–0.88 for Maladaptive Behavior (Survey Form) (0.80s and 0.90s for the Survey Form). Note that interrater reliability coefficients for the Survey and Expanded forms ranged from 0.62 to 0.75. SEM ranged from 3.4 to 8.2 over the four domains, and from 2.2 to 4.9 for the Adaptive Behavior Composite, on the Survey Form.

2.3.2. Rett Assessment Rating Scale

The Rett Assessment Rating Scale (RARS) is used to evaluate subjects with Rett syndrome [12]. The structure of RARS is similar to that of the Childhood Autism Rating Scale (CARS) [13], Gilliam Autism Rating Scale (GARS) [14], and Asperger Syndrome Diagnostic Scale (ASDS) [15], well-known instruments devised to assess the presence/absence of symptoms characterizing the pervasive developmental disorders included in the same nosographic category as RS [16]. The items in RARS were constructed following the diagnostic criteria for RS proposed by DSM-IV-TR [16] and recent research and clinical experience. A total of 31 items were generated as representative of the profile of RS. Each item concerns a specific phenotypic characteristic and describes four increasing levels of its severity. Each item is provided with a brief glossary explaining its meaning in a few words.

Each item is rated on a 4-point scale, where 1 = within normal limits, 2 = infrequent or low abnormality, 3 = frequent or medium-high abnormality, and 4 = strong abnormality. Intermediate ratings are possible; for example, an answer between 2 and 3 points is rated as 2.5 [12]. For each item, the evaluator circles the number corresponding to the best description of the patient. After a patient has been rated on all 31 items, a Total score is computed by summing the individual ratings. This Total score allows the evaluator to identify the level of severity of RS, conceptualized as a continuum ranging from mild symptoms to heavy deficits.

The RARS was established by a standardization procedure, involving a sample of 220 patients with RS, proving that the instrument is statistically valid and reliable. More precisely, normal distribution analyses of the scores were computed, and the mean scores of the scale were similar to the median and the mode. Skewness and kurtosis values, calculated for the distribution of the Total score, were 0.110 and 0.352, respectively. The distribution was found to be normal. Cronbach’s α was used to determine the internal consistency for the whole scale and subscales. Total α was 0.912, and the internal consistency of the subscales was high (0.811–0.934).

2.4. Neuropsychological measures

Eye tracker technology was used to measure recognition, matching of pairs (the same), and semantic categorization (the similar). Three tasks were designed: (1) response to verbal instruction (look at the dog, etc.); (2) recognition and matching of pairs (look at the one that is the same), and (3) semantic categorization (look at the one that is similar). The images used were of objects familiar to the children, according to their parents. Nine different pictures were divided into three groups: fruit—apple, orange, and banana; animals—dog, cat, and horse; and emotions—happy, sad, and angry. Each item was presented for 5 seconds. The parameter was the length (seconds) of fixation.

An Eyegaze device was used to record the subject’s visual scanning response to visual computer screen stimulation. This device records ocular movements such as the location and duration of ocular fixations (i.e., pause of eye movement on an object of interest) and saccadic movements (i.e., rapid movements between fixations) [17] movements between fixations. EyeGaze was used in a microcomputer with a 15-in. LCD monitor and a Matrox-like video plaque, which captures the signals sent from a video camera equipped with lenses sensitive to high-speed infrared light. The camera also has a LED that emits low-intensity infrared light directly on the retina of the person sitting in front of the monitor. The direction of the gaze is determined according to the Pupil Center/Corneal Reflection Method. The software Pas-
Table 1
Clinical, EEG and behavioral characteristics of the patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Age at epilepsy onset (years)</th>
<th>Seizure type</th>
<th>Seizure frequency</th>
<th>AED</th>
<th>Clinical stage</th>
<th>EEG stage</th>
<th>EEG pattern</th>
<th>VABS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RARS (Total score)</th>
<th>MECP2 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>4</td>
<td>Myoclonic</td>
<td>Sporadic</td>
<td>VPA</td>
<td>III</td>
<td>III</td>
<td>Theta activity</td>
<td>118</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>1</td>
<td>Tonic</td>
<td>Controlled</td>
<td>VPA</td>
<td>III</td>
<td>III</td>
<td>Theta activity</td>
<td>110</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>4</td>
<td>Tonic</td>
<td>Controlled (single seizure)</td>
<td>VPA</td>
<td>III</td>
<td>III</td>
<td>FCP spikes</td>
<td>121</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>8</td>
<td>Focal</td>
<td>Monthly</td>
<td>VPA</td>
<td>III</td>
<td>III</td>
<td>Theta activity</td>
<td>89</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>3</td>
<td>Atonic</td>
<td>Weekly</td>
<td>LEV</td>
<td>III</td>
<td>III</td>
<td>FCP spikes</td>
<td>169</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>4</td>
<td>Focal</td>
<td>Sporadic</td>
<td>VPA</td>
<td>III</td>
<td>III</td>
<td>Theta activity</td>
<td>84</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>8</td>
<td>Focal</td>
<td>Sporadic</td>
<td>VPA + LEV</td>
<td>III</td>
<td>III</td>
<td>FCP spikes</td>
<td>123</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>2</td>
<td>Focal</td>
<td>Weekly</td>
<td>VPA</td>
<td>IV</td>
<td>IV</td>
<td>FCP spikes</td>
<td>34</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>6</td>
<td>Focal</td>
<td>Weekly</td>
<td>TPM + PB</td>
<td>III</td>
<td>III</td>
<td>FCP spikes</td>
<td>107</td>
<td>43</td>
<td>17</td>
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<tr>
<td>10</td>
<td>14</td>
<td>6</td>
<td>Tonic</td>
<td>Weekly</td>
<td>VPA + LTG</td>
<td>IV</td>
<td>IV</td>
<td>Theta activity</td>
<td>92</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>3</td>
<td>Generalized tonic–clonic</td>
<td>Monthly</td>
<td>VPA + LTG</td>
<td>III</td>
<td>III</td>
<td>FCP spikes</td>
<td>113</td>
<td>43</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
<td>2</td>
<td>Generalized tonic–clonic</td>
<td>Weekly</td>
<td>VPA + LTG</td>
<td>IV</td>
<td>IV</td>
<td>Diffuse spike–waves</td>
<td>134</td>
<td>49</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>14</td>
<td>Generalized tonic–clonic</td>
<td>Controlled (single seizure)</td>
<td>LTG</td>
<td>IV</td>
<td>IV</td>
<td>Theta activity</td>
<td>113</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>14</td>
<td>18</td>
<td>3</td>
<td>Focal</td>
<td>Sporadic</td>
<td>VPA + LTG</td>
<td>IV</td>
<td>IV</td>
<td>FCP spikes</td>
<td>58</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>19</td>
<td>5</td>
<td>Focal</td>
<td>Weekly</td>
<td>VPA</td>
<td>IV</td>
<td>IV</td>
<td>Theta activity</td>
<td>142</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td>16</td>
<td>19</td>
<td>8</td>
<td>Focal</td>
<td>Daily</td>
<td>CBZ + ZNS</td>
<td>IV</td>
<td>IV</td>
<td>Multifocal spikes</td>
<td>83</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>17</td>
<td>21</td>
<td>2</td>
<td>Focal</td>
<td>Controlled</td>
<td>CBZ</td>
<td>IV</td>
<td>IV</td>
<td>FCP spikes</td>
<td>131</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>18</td>
<td>21</td>
<td>9</td>
<td>Generalized tonic–clonic</td>
<td>Sporadic</td>
<td>LTG</td>
<td>IV</td>
<td>IV</td>
<td>Theta activity</td>
<td>110</td>
<td>24</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> VABS, Vineland Adaptive Behavior Scales; RARS, Rett Assessment Rating Scale; VPA, valproic acid; LEV, levetiracetam; CBZ, carbamazepine; LTG, lamotrigine; TPM, topiramate; PB, phenobarbital; ZNS, zonisamide; FCP, frontocentroparietal.
sive Gaze Tracing (LC Technologies, Inc., Sao Paulo, Brazil) was used to generate eye found flag, gaze point, pupil diameter during visual scanning, and eyeball position. The girls sat on their parent’s lap, about 20 cm away from the monitor.

2.5. Procedure

Each girl underwent, on the same day and in direct succession, EEG video-polygraphic recording during wakefulness and neuro-

*Fig. 1. Rhythmic theta activity recorded mainly in the frontal and central regions.*

*Fig. 2. Asynchronous focal epileptiform activity over both frontotemporal regions.*
psychological assessment with the EyeGaze. Behavioral measures were collected through interviews with parents in a separate session. Informed consent to participate in the study was obtained from parents.

2.6. Data analysis

Total scores were calculated for each neuropsychological and behavioral scale and for each subject. Pearson correlations were
used to assess the relationship of each neurophysiological measure to neuropsychological and behavioral scales. The $P$ value was set at $<0.05$.

3. Results

Results are presented with respect to each of the neurophysiological measures presented above.

3.1. Relationship between age at epilepsy onset and neuropsychological measures

Age at epilepsy onset was positively correlated with the ability of the girls with RS to reply to verbal instructions, to recognize and match pairs, and to semantically categorize animals: $r = +0.43$, $P < 0.05$, $r = +0.43$, $P < 0.05$, and $r = +0.41$, $P < 0.07$, respectively. In addition, age at epilepsy onset was positively correlated with the ability of the girls with RS to reply to verbal instructions related to emotions: $r = +0.64$, $P < 0.01$. According to this result, the later the onset of seizures, the greater the ability to recognize and associate animals and emotions (Fig. 5).

3.2. Relationship between seizure frequency and neuropsychological/behavioral measures

Seizure frequency was negatively correlated with the ability of the girls with RS to reply to verbal instructions, to recognize and match pairs, and to semantically categorize animals: $r = -0.45$, $P < 0.05$, $r = -0.54$, $P < 0.02$, and $r = -0.47$, $P < 0.05$, respectively (Fig. 6). Also, seizure frequency was negatively correlated with the Vineland Adaptive Behavior Scales ($r = -0.49$, $P < 0.03$). Thus, as seizure frequency increased, Vineland Scales Total scores and ability to recognize and associate animals decreased.

3.3. Relationship between EEG stage and neuropsychological/behavioral measures

EEG stage was negatively correlated with the ability of the girls with RS to reply to verbal instructions, to recognize and match pairs, and to semantically categorize animals: $r = -0.47$, $P < 0.05$, $r = -0.43$, $P < 0.06$, and $r = -0.47$, $P < 0.05$, respectively (Fig. 7). In addition, EEG stage was negatively correlated with Vineland Scales Daily Living ($r = -0.55$, $P < 0.02$) and Total ($r = -0.47$, $P < 0.05$) scores. Thus, as EEG stage increased, ability to recognize and associate animals and Vineland Scales scores decreased.

3.4. Relationship between EEG abnormalities and neuropsychological/behavioral measures

EEG abnormalities were negatively correlated with the ability of the girls with RS to reply to verbal instructions, to recognize and match pairs, and to semantically categorize fruit: $r = -0.469$, $P < 0.05$, $r = -0.43$, $P < 0.06$, and $r = -0.48$, $P < 0.05$, respectively. Also, EEG abnormalities were negatively correlated with Vineland Scales General scores ($r = -0.49$, $P < 0.05$) (Fig. 8) and positively correlated with RARS scores ($r = 0.64$, $P < 0.01$). Therefore, as EEG abnormalities became more diffuse and multifocal, Vineland Total scores and the ability to recognize and associate fruit decreased and RARS scores increased.

4. Discussion

Cognitive performance and behavioral features in persons with RS have scarcely been investigated. Most studies on cognitive functions and behavioral features in RS are based on information supplied by the parents and professionals who take care of the patients [18,19]. Few studies have explored cognitive performance directly in subjects with RS: in 2006, Baptista et al. [20] demonstrated that intentional gaze is a measurable parameter in girls with RS and can be used to explore their cognitive performance. More recently, the same authors recommended reevaluation of the method because a small group of 10 girls with RS (aged 4–12 years) did not manifest recognition of the solicited concepts within a fixation time of 4 seconds, even if they argued that the low age of the sample and the brief fixation span could have interfered with the results [21]. Although it is well known that girls
with RS have good visual attention [22], it has recently been shown that they are able to learn to discriminate complex stimuli [23]; however, they have a specific deficit in the ability to attend selectively to relevant sources of information while ignoring irrelevant ones [24].

To our knowledge this is the first study that has demonstrated a strict correlation between neurophysiological features and neuropsychological impairment, using eye tracker technology, in patients with RS. The results of our study demonstrate that both epilepsy features (age at seizure onset and seizure frequency) and EEG characteristics (EEG stage and EEG abnormality pattern) are correlated with the ability to recognize and match pairs and semantically categorize with respect to animals and behavioral features, as assessed with the Vineland Scales and RARS. The significant ability to recognize and categorize animals, but not the other objects proposed in the task, may be explained by these girls’ better knowledge of animals as compared with fruits and emotions.

Our findings are coherent both within neurophysiological parameters and within neuropsychological and behavioral measures (as Vineland Scales scores decrease, RARS scores and eye tracking-derived measures increase).

Regarding the relationship between age at epilepsy onset and cognitive impairment, our study shows that also in girls with RS, epilepsy plays a crucial role in future cognitive performance, as demonstrated by recent studies supporting the assumption that the epileptic process underlying seizures could interfere with cognitive development [25]. In addition, in our group of patients with RS, age at seizure onset was inversely correlated with the ability to recognize emotions, as it has been exhaustively shown in patients with temporal lobe epilepsy, in whom early onset of seizures/epilepsy is a key factor leading to severe impairment in recognition of emotions, involving the temporomedial structures and especially the amygdala [26]. This is also supported by the recent finding in a mouse model in which specific deletion of MeCP2 in the basolateral amygdala mediated behavioral phenotypes associated with RS impacting selective forms of learning and memory [27].

With respect to seizure frequency, factors influencing the course of epilepsy in RS are not yet well understood. It has been shown that compared with later onset, early epilepsy onset tends to be associated with more severe epilepsy, including more seizure types, more frequent intractable epilepsy, and status epilepticus [28]. Moreover, children with RS with early developmental problems as well as those with greater motor disability have a higher seizure frequency [29].

Our results in girls with RS with drug-resistant seizures are in accordance with data from the literature demonstrating that repeated seizures are associated with increased intellectual impairment [9].

Looking at EEG features, we found that as soon as EEG abnormalities became more diffuse and multifocal, cognitive performance decreased. This finding could be explained by assuming that epileptiform EEG discharges could have additional effects on cognitive processes (alertness, mental speed) that might accumulate over time, resulting in stable effects [30].

Adverse cognitive side effects, mainly on attention, vigilance, memory, and psychomotor speed, have been reported with AEDs [31,32]. All but one patient in our sample were on AEDs, but we could not find a close relationship between cognitive impairment and the use of a specific AED.

Our preliminary findings on a limited number of patients indicate that in the clinical management of RS, epilepsy characteristics and EEG patterns suggestive of epileptic encephalopathy should be considered prognostic factors in neuropsychological outcome.

Future investigations focused on the correlation between neurophysiological features and definite phases of information processing, attention, memory, and logic relationships in RS are needed to correlate in more depth the exact stage of information processing impairment with neurophysiological features. Finding that this relationship is strongest in the input phase (i.e., attention process), we could focus on cognitive empowerment in this precise phase. With reference to the severity of the disease and to the difficulty in distinguishing the different phases of information processing, we know that new paradigms could allow us to attribute disease to one specific phase [23,24].

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References


