Ghrelin improves dystonia and tremor in patients with Rett syndrome: A pilot study

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ABSTRACT

Background: Dystonia occurs in approximately 60% of patients with Rett syndrome (RTT) and severely impairs their quality of life. However, an effective standard therapy has not been established. In a previous study, ghrelin levels were significantly decreased in patients with RTT, in particular, among patients over 10 years old. This prompted speculation that ghrelin may play an important role in RTT.

Objectives: Four patients, including two adults, with severe dystonia and tremor, were recruited.

Methods: Ghrelin was intravenously administered at a dose of 3 μg/kg, once-daily for 3 days, followed by once every 3 weeks. Objective evaluation was performed, including scoring for different clinical features (SDCF), the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Visual Analog Scale (VAS).

Results: The SDCF, BFMDRS, autonomic dysfunction and VAS scores were markedly improved in two patients with severe dystonia and head tremor.

Conclusion: Ghrelin may improve extrapyramidal symptoms in patients with RTT.

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1. Introduction

Rett syndrome (RTT), a neurodevelopmental disorder that mainly affects females, is caused by mutations in the MECP2 gene. It is characterized by normal early development, followed by the loss of psychomotor skills and acquired purposeful hand skills, and the onset of stereotypic hand movements and gait disturbances [1–5]. Extrapyramidal involvement manifests as stereotypic movements, dystonia, Parkinsonian tremor, rigidity, and hypokinesia. Dystonia occurs in 59.0% to 63.3% of patients with RTT and more severely affects patients older than 8 years [6–8]. Although both generalized and focal dystonia reduce the patients’ quality of life and motor functioning, apparent life-threatening episodes are also observed in RTT [9]. Few reports have shown improvements in dystonia and autonomic dysfunction in patients with RTT [9]. Various candidate drugs have been studied, including the muscarinic cholinergic antagonist trihexyphenidyl and dopamine agonists; however, these agents failed to ameliorate dystonia, tremor and autonomic dysfunction.

Ghrelin, a 28-amino acid peptide isolated from the stomach as an endogenous ligand for growth hormone secretagogue receptor 1a (GHS-R), is expressed in both the stomach and hypothalamus [10]. It has multiple physiological actions, including stimulating somatic growth, increasing appetite [11], enhancing gut motility, and regulating autonomic function [12], notably, the activity of the sympathetic nervous system and the stress response [12]. According to some reports, GHS-R is expressed in the central nervous system and regulates dopamine signalling [13].

As shown by previous research, the biological activity of ghrelin and its localization are related to clinical phenotypes of RTT. Plasma levels of ghrelin were decreased, particularly, in patients older than 10 years [14, 15]. Thus, it was speculated that ghrelin may play an important role in the pathophysiology of RTT. The present study enrolled four RTT patients with confirmed MECP2 mutations, who were intravenously administered ghrelin.

2. Patients and methods

2.1. Patients

The study enrolled four Japanese females with RTT, aged between 12 and 32 years (mean 21.75 ± 8.18 years). Each patient had an MECP2 mutation and was diagnosed as having RTT. Patient information,
including activity levels in daily life, clinical symptoms and signs, distribution of dystonia, drug treatments, including antiepileptic drugs, dopamine, antimuscarinic cholinergic agents, is shown in Table 1. The study protocol was approved by the Institutional Review Board of Kurume University. All patients provided written informed consent to participate in this study.

2.2. Study design

Patients were hospitalized for 7 days in Kurume University Hospital (Kurume city, Japan). The pre-treatment period was defined as 2 days before ghrelin administration. Ghrelin was intravenously administered at a dose of 3 μg/kg for 5 min, once-daily for 3 days. Thereafter, for patients 1 and 2, who exhibited dystonia, received the same dose of intravenous ghrelin was administered over 2 days every 3 weeks. These patients were clinically evaluated on multiple occasions (see Fig. 1).

2.3. Ghrelin

Synthetic human ghrelin (active form) was obtained from Peptide Institute Inc. (Osaka, Japan) and prepared as described in a previous report [16–22]. Examination by Japan Food Research Laboratories (Tokyo, Japan) did not find any traces of endotoxin in the ghrelin solution. In brief, recently applied clinical regimens of ghrelin administration were modified. Serum growth hormone (GH) and IGF-1 levels were measured before and after ghrelin administration.

2.4. Biochemistry and endocrinology parameters

Blood samples for measurement of biochemical and endocrine parameters were taken in the morning on day 1 of ghrelin treatment, after an overnight fast of at least 10 h. For ghrelin assays, blood samples were collected in tubes containing 1-mg/ml EDTA-2Na and 500-U/mL aprotinin. After immediate centrifugation at 4 °C, the plasma samples were acidified by 1 normal HCL and stored at −80 °C. A fluorescent enzyme immunoassay was utilized to measure GH levels. An immununoradiometric assay (SRL Co Ltd., Tokyo, Japan) was utilized to measure serum IGF-1 levels. Plasma levels of intact and des-octanoyl ghrelin were measured with an Active Ghrelin and Desacyl-Ghrelin ELISA kit (LSI Medience Corporation, Tokyo, Japan).

2.5. Clinical evaluation of ghrelin treatment

Objective evaluations were performed, including scoring for different clinical features (SDCF), which consists of comprehensive clinical and neurological findings [1]. The score ranges from 0 to 40, with 40 points being the worst score. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) score (range of 0 to 120) was assessed by two pediatric neurologists (KY, TM), with lower scores corresponding to less dystonia [23,24]. The Visual Analog Scale (VAS) was administered by caregivers and physical therapists [25], and scored between 1 and 10, with lower scores corresponding to more severe dysfunction.

3. Results

At the cut-off date for this report, patients 1 and 2 had continued to receive intravenous ghrelin injections. Patient 1 had been followed for 2 years and patient 2 for 10 months. Patients 3 and 4 received ghrelin for only the first 3 days. This was because their parents had other children, and consent was only given for the first 7 days of hospital admission and follow-up at 1 month.

3.1. Changes in biochemistry and endocrinology parameters

During this study, complete blood count, and liver and kidney function were not significantly changed. Plasma levels of active and des-acyl ghrelin, before and after ghrelin administration, are shown in Table 2. After ghrelin administration, plasma ghrelin levels displayed an increase after 15 min, followed by a gradual decline until 90 min. Plasma levels of active ghrelin in the four patients were 25.1, 34.7, 20.6, and 60.6 before ghrelin administration, with an immediate rise to 3384.0, 9749.6, 10,562.0, and 11,361.9, respectively, within 15 min after ghrelin administration. In the four patients, GH levels changed from 0.2, 3.0, 2.9, and 0.6 ng/ml, respectively, before ghrelin administration, to peak levels of 35.0, 24.2, 89.9, and 18.1 ng/ml, respectively, after ghrelin administration. Changes in IGF-1 levels were from 214 to 168 ng/ml, 175 to 193 ng/ml, and 285 to 244 ng/ml, in Patients 1, 2, and 3, respectively. Data were not obtained from Patient 4. Neither glucose levels nor serum IGF-1 levels were significantly changed.

Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age on entry (yrs)</td>
<td>21</td>
<td>32</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Typical RTT</td>
<td>Atypical RTT</td>
<td>Typical RTT</td>
<td>Typical RTT</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>150</td>
<td>147</td>
<td>133</td>
<td>122</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>29</td>
<td>55</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>12.9</td>
<td>25.5</td>
<td>18.1</td>
<td>12.8</td>
</tr>
<tr>
<td>ADL</td>
<td>Bedridden</td>
<td>Standing up</td>
<td>Bedridden</td>
<td>Can roll over but often bedridden</td>
</tr>
<tr>
<td>Oral feeding and gastric stoma feeding</td>
<td>Oral feeding by mother</td>
<td>Oral feeding by mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Scoliosis</td>
<td>Agitation</td>
<td>Breathing abnormalities seizure</td>
<td>Breathing abnormalities</td>
</tr>
<tr>
<td>Difficulties in opening mouth</td>
<td>Tremor of the head and hands</td>
<td>Constipation</td>
<td>Conspiration</td>
<td></td>
</tr>
<tr>
<td>Tremor of the head and hands VRM</td>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>Neck, shoulder, and trunk rotation</td>
<td>Right lower extremities, right side of the face, chest, trunk</td>
<td>CBZ, VPA, CLB</td>
<td>CBZ, VPA, CLB</td>
</tr>
<tr>
<td>AEDs</td>
<td>CBZ, VPA, CLB</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>Pramipexol</td>
<td>L-DOPA</td>
<td>CBZ, VPA, CLB</td>
<td>CBZ, VPA, CLB</td>
</tr>
<tr>
<td>Muscarinic cholinergic antagonist</td>
<td>Trihexyphenidyl</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>RTT: Rett syndrome, ADL: active daily life, SDCF: scoring for different clinical features, a score of 0 represents no signs and the worst score was 40, BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale, 0 represents no dystonia with higher scores representing more severe dystonia, VMR: vasomotor reflex, AEDs: antiepileptic drugs, CBZ: carbamazepine, VPA: valproic acid, CLB: clobazam, LEV: levetiracetam, yrs.: years.</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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