

# Correlation Between *Dysphagia* and Malocclusion in Rett Syndrome

## A preliminary study

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### الترباط بين عسر البلع وسوء الإطباق في متلازمة ريت دراسة أولية

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**ABSTRACT: Objectives:** Rett syndrome (RS) is a severe neurological developmental disorder characterised by stereotypical hand movements, epileptic seizures, craniofacial dysmorphism and digestive dysfunction. This study aimed to examine the correlation between the severity of malocclusion and *dysphagia* in patients with RS. **Methods:** This preliminary study was conducted at the Ear, Nose & Throat Clinic of the University Hospital of Siena, Siena, Italy, from January 2014 to December 2017. A total of 56 patients with RS were examined and grouped according to the severity of *dysphagia* (absent, mild, moderate or severe) and malocclusion (<2 mm, 2–3 mm, 3–4 mm or >4 mm). **Results:** All of the patients were female and the mean age was 11.3 years. Eight (14.3%) patients had mild, 18 (32.1%) had moderate and 30 (53.6%) had severe *dysphagia*. Four (7.1%) patients had <2 mm occlusion, 10 (17.9%) had 2–3 mm occlusion, 26 (46.4%) had 3–4 mm occlusion and 16 (28.6%) had >4 mm occlusion. Mild *dysphagia* was observed in 100% and 40% of patients with <2 and 2–3 mm malocclusion, respectively, while moderate *dysphagia* was present in 60% and 38.5% of patients with 2–3 and 3–4 mm malocclusion, respectively. Severe *dysphagia* was observed in 28.6% and 87.5% of patients with 3–4 and >4 mm malocclusion, respectively. There was a significant correlation between *dysphagia* and malocclusion severity ( $P < 0.001$ ). **Conclusion:** A higher degree of malocclusion was associated with more severe *dysphagia* among a cohort of patients with RS.

**Keywords:** X-Linked Mental Retardation; Rett Syndrome; Dysphagia; Malocclusion; Feeding and Eating Disorders of Childhood.

**المخلص:** الهدف: متلازمة ريت هي اضطراب نمو عصبي حاد يتميز بحركات يد نمطية ونوبات من صرع وتشوهات القحف والوجه وخلل الأداء الهضمي. تهدف هذه الدراسة إلى فحص علاقة الإرتباط بين شدة سوء الإطباق وعسر البلع عند مرضى متلازمة ريت. **الطريقة:** أجريت هذه الدراسة الأولية في عيادة الأذن والأنف والحنجرة في مستشفى جامعة سيينا، سيينا، إيطاليا، من يناير 2014 إلى ديسمبر 2017. تم فحص ما مجموعه 56 مريضا من متلازمة ريت وتم تجميعهم وفقا لشدة عسر البلع (غير موجود، بسيط، متوسط، أو شديد) سوء الإطباق (<2 ملم، 2-3 ملم، 3-4 ملم و >4 ملم). **النتائج:** جميع المرضى كانوا من الإناث وكان متوسط العمر 11.3 سنة. كان ثمانية (14.3%) من المرضى مصابين بعسر بسيط، 18 (32.1%) لديهم عسر متوسط و 30 (53.6%) لديهم عسر بلع شديد. أربعة (7.1%) من المرضى كان لديهم إطباق <2 ملم، 10 (17.9%) لديهم إطباق 2-3 ملم، 26 (46.4%) كان لديهم إطباق 3-4 ملم و 16 (28.6%) لديهم إطباق >4 ملم. لوحظ وجود عسر البلع البسيط في 100% و 40% من المرضى الذين يعانون من سوء الإطباق <2 و 2-3 ملم، على التوالي، في حين أن عسر البلع المتوسط كان موجود في 60% و 38.5% من المرضى الذين يعانون من 2-3 و 3-4 ملم سوء الإطباق، على التوالي. ولوحظ عسر البلع الشديد في 28.6% و 87.5% من المرضى مع 3-4 و >4 ملم سوء الإطباق، على التوالي. كانت هناك علاقة إرتباط ملحوظة بين عسر البلع وشدة سوء الإطباق ( $P < 0.001$ ). **الخلاصة:** درجة أعلى من سوء الإطباق كانت مترابطة مع عسر البلع الأكثر شدة بين عينة المرضى المصابين بمتلازمة ريت.

الكلمات المفتاحية: التخلف العقلي المرتبط بالجنس؛ متلازمة ريت؛ عسر البلع؛ سوء الإطباق؛ التغذية واضطراب الأكل عند الأطفال.

#### ADVANCES IN KNOWLEDGE

- The findings of this study indicate that a high degree of malocclusion is associated with more severe *dysphagia* in patients with Rett syndrome.

#### APPLICATION TO PATIENT CARE

- Correcting malocclusion may improve the oral preparatory phase of swallowing, thereby enabling patients with feeding and eating disorders to have a natural diet. This reduces the risk of ab ingestis pneumonia and offers a recourse to percutaneous endoscopic gastrostomy, thus improving the patient's quality of life.

**R**ETT SYNDROME (RS) IS A RARE NEUROLOGICAL disorder which occurs in approximately one in 10,000 live births and develops almost exclusively among females due to an X-linked dominant mutation.<sup>1,2</sup> First described by Andreas Rett in 1966, RS is the second most common cause of mental retardation in females after Down's syndrome.<sup>1,3</sup> Classical RS, the most common form, is characterised by a mutation in the *methyl-CpG-binding protein 2* gene.<sup>4</sup> The diagnosis is mostly based on clinical characteristics, clinical course and genetic/molecular testing.<sup>1,2</sup> In addition, other atypical forms of RS may present with different symptoms and/or mutations.<sup>4,5</sup>

The disease is characterised by abnormal hand movements, epileptic seizures, craniofacial dysmorphism and digestive system problems.<sup>1</sup> Affected patients appear to develop normally until two years of age, at which point they begin to manifest motor and speech disabilities. In addition, the syndrome can present with autism, *ataxia* and intermittent hypoventilation.<sup>1</sup> The condition subsequently stabilises and patients can live to adulthood. Hagberg defined four stages of classical RS: (1) early-onset stagnation marked by delayed developmental milestones; (2) developmental regression with a loss of acquired skills/communication and signs of mental retardation; (3) apparent walking difficulties and slow neuromotor regression; and (4) late motor deterioration resulting in complete wheelchair dependency, weight loss and skeletal deformities.<sup>6</sup>

Patients with RS often have feeding and digestive problems aggravated by poor *bolus* preparation/propulsion, respiratory anomalies, ineffective tongue movements, incomplete chewing and head and neck dysmorphism (e.g. advancement of the *maxilla*, neuromuscular insufficiency and back deformities).<sup>6-12</sup> Dental anomalies are also common, such as open bite due to the absence of vertical overlap/contact between the anterior maxillary and mandibular teeth and malocclusion resulting from unfavourable growth patterns and incorrect mandibular positioning associated with exacerbated open-mouth breathing and tongue thrusting habits [Figure 1].<sup>7,13,14</sup> Bruxism is also a typical feature, although it is not pathognomonic. The current study aimed to evaluate oral and dental characteristics in a series of patients with RS in order to determine a correlation between the severity of malocclusion and *dysphagia*.

## Methods

This preliminary study was conducted at the Ear, Nose & Throat (ENT) Clinic of the University Hospital of Siena, Siena, Italy, from January 2014 to December 2017. A total of 56 patients with classical RS admitted to the ENT Clinic were randomly enrolled in the study. Various clinical examinations were conducted during hospitalisation, including history-taking, body weight and height measurements as well as laryngological, ENT, speech and dental evaluations. Patients were also monitored during mealtimes and underwent evaluations by a speech therapist. In addition, detailed feeding histories were taken from parents/caregivers during interviews. The same speech therapist evaluated all of the patients so as to ensure reliable results. The perioral tissue, oral *mucosa* and tongue of each patient was assessed by a dentist.

As part of the laryngological evaluation, the patients underwent a partial fiberoptic endoscopic evaluation of the *pharynx* and *larynx* during and after the act of swallowing for the detection of uncontrolled *bolus*, piecemeal deglutition, premature loss of liquid, vallecular and pyriform sinus residue, aspiration and absence of cough reflex. However, due to poor patient compliance, only a partial endoscopic assessment of swallowing could be performed to establish the severity of *dysphagia*. The endoscopic evaluation was performed without anaesthesia while the patient was at rest after being fed 2–3 spoons of a semi-liquid *bolus* of water gel.

All patients were classified according to *dysphagia* severity. Mild *dysphagia* was defined as slight coughing while eating, oral leakage/drooling, no choking, no vocal fold alterations, good laryngeal sensitivity and minimal stagnation of secretions in the pyriform sinuses.<sup>7,13</sup> Moderate *dysphagia* was indicated by delayed pharyngeal clearance of vallecular and pyriform sinus secretions, abundant coughing after eating, slow laryngeal sphincter function and a high risk of aspiration. Finally, severe *dysphagia* was defined as an absence of coughing, ineffective pharyngeal clearance, permanent post-swallow residue, premature loss of liquid or uncontrolled *bolus*, poor deglutitive airway protection and a very high risk of aspiration.<sup>7,13</sup> Patients with normal swallowing were deemed not to have any *dysphagia*.



**Figure 1:** Photographs of a 14-year-old girl with Rett syndrome showing typical dental features of (A) maxillary advancement and (B) maxillary protrusion, resulting in (C) misalignment of the maxillary and mandibular teeth (i.e. malocclusion).

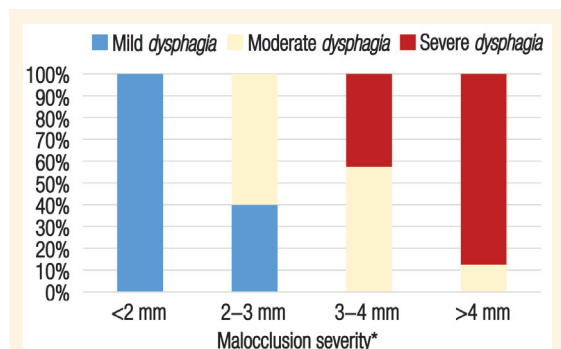
**Table 1:** Oral and dental characteristics of patients with Rett syndrome admitted to the University Hospital of Siena, Siena, Italy (N = 56)

Characteristic	n (%)
Open bite	50 (89.3)
Open-mouth breathing	46 (82.1)
Drooling	52 (92.9)
Reduced lip continence	56 (100)
Bruxism	48 (85.7)
Involuntary tongue movements	46 (82.1)
Poor lateralisation of the tongue	52 (92.9)

**Table 2:** Severity of malocclusion and *dysphagia* among patients with Rett syndrome admitted to the University Hospital of Siena, Siena, Italy (N = 56)

Dysphagia severity	Malocclusion severity*, n (%)			
	<2 mm (n = 4)	2–3 mm (n = 10)	3–4 mm (n = 26)	>4 mm (n = 16)
Mild	4 (100)	4 (40)	0 (0)	0 (0)
Moderate	0 (0)	6 (60)	10 (38.5)	2 (12.5)
Severe	0 (0)	0 (0)	16 (28.6)	14 (87.5)

\*Defined as the distance between the mesiobuccal cusp of the maxillary first molar and mesiobuccal groove of the mandibular first molar in the sagittal plane.



**Figure 2:** Severity of malocclusion and *dysphagia* among patients with Rett syndrome admitted to the University Hospital of Siena, Siena, Italy (N = 56).

\*Defined as the distance between the mesiobuccal cusp of the maxillary first molar and mesiobuccal groove of the mandibular first molar in the sagittal plane.

Occlusion was categorised using Angle's classification according to the relationship between the mesiobuccal cusp of the maxillary first molar and the mesiobuccal groove of the mandibular first molar.<sup>15</sup> Class I was defined as the alignment of the mesiobuccal cusp of the maxillary first molar with the mesiobuccal groove of the mandibular first molar (i.e. neutral or normal occlusion). Class II was indicated in cases wherein the mesiobuccal groove of the lower first molar aligned posteriorly to the mesiobuccal cusp of the maxillary first

molar (i.e. distocclusion).<sup>15</sup> Depending on the position of the anterior teeth, patients with class II occlusion were subdivided into either division one (proclined upper incisors) or two (lingually inclined upper central incisors possibly overlapped by the upper later incisors). For class III occlusion, the mesiobuccal groove of the mandibular first molar aligned anteriorly to the mesiobuccal cusp of the maxillary first molar (i.e. mesiocclusion).<sup>15</sup> Malocclusion severity was assessed in terms of the distance between the mesiobuccal cusp of the maxillary first molar and mesiobuccal groove of the mandibular first molar in the sagittal plane (<2 mm, 2–3 mm, 3–4 mm or >4 mm).

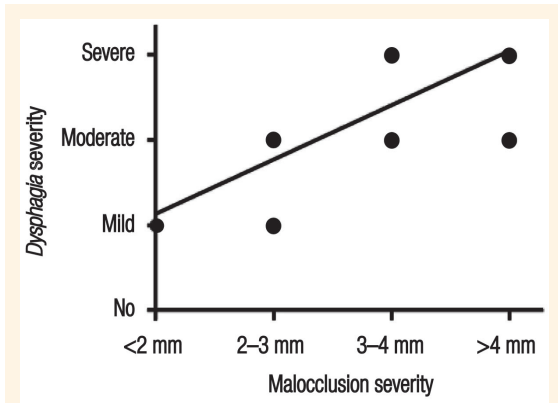
Data were analysed by linear regression using Graph Pad Software (GraphPad Software Inc., La Jolla, California, USA). A *P* value of <0.001 was considered statistically significant. This study was approved by the local ethics committee of the Tuscany Region Area Vasta Sud Est (#22.1.14). Both parents or legal guardians of each patient provided informed written consent for their participation in the study.

## Results

All 56 patients were female. The mean age was 11.3 years (range: 8–17 years old) and the patients resided in the southern (59%), central (22%) and northern (19%) regions of Italy. All cases showed an early arrest in growth associated with body weight below the lower limit of their peers (<28 and <36 kg for 8–10- and 11–17-year-olds, respectively). In total, 39 (69.6%) patients were taking anti-epileptic medications.

All of the patients had some form of *dysphagia*, with eight (14.3%) patients with mild, 18 (32.1%) with moderate and 30 (53.6%) with severe *dysphagia*. Reduced lip consistency and uncontrolled tongue movements hindered chewing and *bolus* preparation, making feeding slow. Swallowing dysfunction and upper gastrointestinal motility disorders were associated with other anomalies, including gastroesophageal reflux disease (60.7%) and a history of recurrent bronchitis (85.7%), aspiration (14.3%) and *ab ingestis* pneumonia requiring percutaneous endoscopic gastrostomy (PEG; 3.6%). Open bite was identified in 50 (89.3%) patients [Table 1].

All of the patients had Angle's class II malocclusion. Four (7.1%) patients had <2 mm malocclusion, 10 (17.9%) had 2–3 mm malocclusion, 26 (46.4%) had 3–4 mm malocclusion and 16 (28.6%) had >4 mm malocclusion. Overall, all patients with <2 mm malocclusion and 40% of patients with 2–3 mm malocclusion had mild *dysphagia*, while 60% and 38.5% of patients with 2–3 and 3–4 mm malocclusion, respectively, had moderate *dysphagia*. Severe *dysphagia* was observed



**Figure 3:** Chart showing a statistically significant correlation ( $P < 0.001$ ) between *dysphagia* and malocclusion severity among patients with Rett syndrome admitted to the University Hospital of Siena, Siena, Italy (N = 56).

in 28.6% and 87.5% of patients with 3–4 and >4 mm malocclusion, respectively [Table 2 and Figure 2]. According to a linear regression analysis, there was a statistically significant correlation between *dysphagia* and malocclusion severity ( $P < 0.001$ ) [Figure 3].

## Discussion

Swallowing is a complex biological process, with the oral preparatory and propulsive stages closely linked to events in the pharyngeal phase.<sup>7,13,16–18</sup> The oral phase begins when the tongue pushes the *bolus* up and posteriorly towards the oropharynx. The propulsive action of the tongue is the result of the centripetal movement of the central groove of the tongue with the tip pressed against the hard palate and the sides of the tongue contacting the oral phase of the upper dental arch. The process lasts less than a second and involves closing the lips to prevent the *bolus* falling laterally. The jaw is normally kept closed by the action of the temporal, masseter, internal pterygoid and external pterygoid muscles.

Since the tongues of RS patients tend to move repetitively up and down without creating enough compression against the palate to push the *bolus* into the pharynx, the palate has a poor glossopharyngeal seal resulting in the escape of liquids from the mouth into the *pharynx* (i.e. pharyngeal spillover and the premature fall of *bolus*). An incorrect tongue position and irregular tongue movements inevitably aggravate maxillary protrusion. Advancement of the *maxilla* makes it difficult to move the tongue towards the *oropharynx*, resulting in the lateral leakage of food. This condition is often aggravated by lip incontinence due to hypotonia of the *orbicularis* muscles.

All patients with RS have structural and functional abnormalities that impair the oral phase, such as

reduced lip continence, drooling, open-mouth breathing, involuntary tongue movements, open bite, growth defects of the *maxilla*, incorrect mandibular positioning and neurogenic scoliosis with double curve deformation.<sup>6–9</sup> Molina-García *et al.* found that anterior open bite, ogival palate, bruxism, open-mouth breathing and tongue thrusting were common in patients with RS.<sup>19</sup> Fuertes-González *et al.* reported diurnal bruxism to be the most frequent oral habit of patients with RS, followed by stereotypical tongue movements and open-mouth breathing.<sup>14</sup> Despite a decreased incidence of caries compared to the control group, RS patients also had greater periodontal alterations and an increased prevalence of drooling, dental wear, high-arched palates and anterior open bite.<sup>14</sup> In addition, RS patients often demonstrate digit sucking and orofacial motor functional disorders; in the early stages of the disease, these characteristics can give rise to malocclusions such as anterior open bite and a high-arched palate.<sup>20</sup>

To the best of the authors' knowledge, this preliminary study is the first to show a significant association between malocclusion and *dysphagia* severity in patients with RS. Although there are many causes of *dysphagia* in patients with RS, malocclusion is an obvious impediment to the oral phase of physiological swallowing. In the current study, a higher degree of malocclusion was found to be associated with more severe *dysphagia*, with an increase in the degree of misalignment of the maxillary and mandibular teeth corresponding to a more severe degree of *dysphagia*. Presumably, correcting the malocclusion could potentially reduce the severity of *dysphagia* and promote a normal diet, delaying the risk of *ab ingestis* pneumonia and PEG, thus improving the patient's quality of life.

Unfortunately, initiating such corrective measures for patients with RS is complex and often logistically difficult due to postural requirements and lack of patient cooperation during radiological procedures. Should future techniques allow X-rays to be taken in different positions, it might be possible to undertake appropriate interventions to correct malocclusion and tongue position in patients with RS. However, it is important to reiterate that malocclusion is only one possible cause of *dysphagia* in RS; therefore, the correction of malocclusion alone may not completely eliminate *dysphagia* in RS patients. It is therefore recommended that further research be undertaken to evaluate malocclusion in a larger sample of RS patients.

## Conclusion

This preliminary study showed a significant correlation between malocclusion and *dysphagia* in patients with RS, with a higher degree of malocclusion associated with



more severe *dysphagia*. Based on these findings, it can be postulated that correction of the malocclusion would result in improvements in the oral preparatory phase of swallowing and, therefore, in *dysphagia* severity. This would promote a normal diet, delaying the risk of *ab ingestis* pneumonia, ultimately improving the patient's quality of life. However, it is important to note that malocclusion is only one possible cause of *dysphagia* in RS and therefore such corrective measures may prove insufficient to treat affected patients.

#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

#### FUNDING

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