Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology 31 (2019) 350–355

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Case Report

Idiopathic first bite syndrome treated with Rikkosan: A case report

Kamichika Hayashi*, Takeshi Onda, Satoru Ogane, Takashi Kamio, Hitoshi Ohata, Nobuo Takano, Takahiko Shibahara

Department of Oral and Maxillofacial Surgery, Tokyo Dental College Chiba Dental Center, 1-2-2 Masago, Mihama-ku, Chiba 261-8502, Japan

ARTICLE INFO

Keywords:
First bite syndrome
Rikkosan
Parotid gland
Sympathetic nerve
Parasympathetic nerve

ABSTRACT

First bite syndrome (FBS)is characterized by sharp pain in the parotid region at the first bite of a meal which gradually decreases as mastication continues, and is thought to be caused by sympathetic nerve damage. When FBS occurs with no history suggestive of nerve damage, it is classified as idiopathic. A case of idiopathic FBS that was treated effectively with Rikkosan is presented. The patient was an 81-year-old woman who developed sharp pain in the left parotid region with the first bite of every meal in November 2015. With no specific findings, the initial diagnosis was trigeminal neuralgia, but carbamazepine was ineffective. In February 2016, temporomandibular disorder was diagnosed as the cause of masticatory muscle pain and was treated with splinting and loxoprofen sodium, but this was also ineffective. In June 2016, a panoramic radiograph, plain craniocervical magnetic resonance imaging, and blood tests were all negative. Idiopathic FBS was diagnosed and treated by gargling and swallowing Rikkosan before meals and eating bitter or sweet foods first, followed by salty or sour foods. The FBS improved, and after 1 week, she had days with no pain. Rikkosan was discontinued after a month leading to immediate recurrence. The patient was instructed to use half the dose of Rikkosan, which was effective with no side effects. In October 2016, the patient started gargling with Rikkosan. In March 2017, the Rikkosan was discontinued and the dietary strategy was continued with no further recurrence. In this case, idiopathic FBS improved with Rikkosan treatment.

1. Introduction

The clinical symptoms of first bite syndrome (FBS) are sharp pain in the parotid region at the first bite of a meal, which gradually decreases as mastication continues. In 1986, Haubrich [1] described these symptoms, after which Netterville et al. [2] coined the term “first bite syndrome.” FBS has been reported as a complication of surgery in the parapharyngeal space [3–6] and of parotid gland surgery and neck dissection [1,7,8]. A case of FBS that developed after bilateral maxillary osteotomy has been reported recently [9], and according to the authors, this was the first case of FBS developing after bilateral temporomandibular joint replacement [10]. FBS is thought to be caused by sympathetic nerve damage [2,4,5,11], but the details remain unclear. When symptomatology similar to that seen in FBS occurs in the absence of any event in the past medical history that may have caused nerve damage, it is referred to as idiopathic FBS [12,13].

Here we present a case of idiopathic FBS that was treated effectively by gargling with the *kampo* medicine Rikkosan is presented and discussed possible mechanisms of onset of idiopathic first bite syndrome and the effectiveness of Rikkosan.

2. Case report

The patient was an 81-year-old woman with a chief complaint of pain in the left parotid region who was first seen in June 2016. Her past medical history included hypothyroidism (currently taking levothyroxine), angina pectoris (currently taking nicorandil), hypertension (currently taking amlodipine), and dyslipidemia (currently taking fluvastatin). There was nothing of note in her family history.

Starting around November 2015, she had sharp pain in the left parotid region when taking the first bite of a meal. She was examined at a local otolaryngology department in December 2015, and no structural changes were found in the parotid region or pharyngeal region. The patient was diagnosed with trigeminal neuralgia and carbamazepine was prescribed, but it was ineffective even at a dose of 600 mg/day.

Because the symptoms did not improve, the patient was examined at a local dental clinic in February 2016. Temporomandibular disorder was diagnosed as the cause of masticatory muscle pain. A splint was applied and loxoprofen sodium 60 mg was prescribed to be taken as needed for masticatory muscle pain. The symptoms continued thereafter, with sharp pain in the left parotid region on the first bite of each

* Corresponding author.
E-mail address: hayashikamichika@tdc.ac.jp (K. Hayashi).

https://doi.org/10.1016/j.ajoms.2019.03.011
Received 8 November 2018; Received in revised form 19 January 2019; Accepted 29 March 2019
Available online 31 August 2019

meal which gradually improved as mastication continued. The patient became less inclined to eat because of the pain at the start of every meal.

The patient visited our department in June 2016 for a full examination and treatment in order to improve her dietary quality of life. A panoramic X-ray radiograph was taken, and plain craniocervical magnetic resonance imaging (MRI) and blood tests were performed.

2.1. Presentation

She had sharp pain in the parotid region at the first bite of every meal, with the first bite at breakfast being the most painful. The pain gradually lessened as mastication continued and disappeared after about 1 min. No spontaneous pain was reported. Pain occurred only in response to taste stimulation of the tongue, and was particularly intense with sour taste stimuli. There was no pain on speaking or simply opening and closing the mouth. No signs of Frey's syndrome or gustatory sweating were noted.

The face was bilaterally symmetrical with no swelling or redness. There was no swelling or tenderness of the parotid gland or submandibular gland. No trigger points were detected in the face or masticatory muscles. No neuroparalysis was found.

On intraoral examination, no carious teeth or teeth that could be the cause of a dental focus of infection were found. There was no gingival swelling or structural changes in the mouth. No swelling or tenderness was found on the floor of the mouth. A gum test showed salivation of 12 ml in 10 min.

No focus of infection that could have been the cause of the patient's pain was found in the mandible on panoramic X-ray. No deformation of the mandibular condyle and no salivary duct calculi were found (Fig. 1). There were no findings indicative of salivary calculi on a radiograph taken at a tangent to the left parotid gland (Fig. 2).

No vascular anomaly displacing the trigeminal or glossopharyngeal nerve was evident on MRI. There were no signs of a tumor or inflammation of the parotid gland, masseter muscle, pharyngeal space, or neck region. No obstruction of the major parotid gland ducts or segmental dilation was found, and no imaging findings indicated salivary leak. There were no findings of maxillary or mandibular osteomyelitis (Figs. 3 and 4).

Laboratory investigations revealed the following: white blood cell count, 5600/μl; red blood cell count, 4,280,000/μl; platelet count, 227,000/μl; hemoglobin, 12.9 g/dl; hematocrit, 37.9%; C-reactive protein, 0.07 mg/dl; amylase, 89 U/l; sedimentation rate, 15 mm; fasting blood glucose, 105 mg/dl; and HbA_{1c} (National Glycohemoglobin Standardization Program [NGSP]), 5.7%. There were no abnormal values indicating hepatic or renal dysfunction.

The clinical diagnosis was idiopathic FBS.

2.2. Treatment and clinical course

From June 2016, the patient was instructed to dissolve approximately 1.0 g Rikkosan in 100 ml hot water, to hold the resulting mixture in the mouth for 30 s, gargle, and then swallow it before meals as treatment for idiopathic FBS (Fig. 5). The patient was also instructed to eat bitter-tasting or sweet-tasting foods first, followed by salty or sour foods. The idiopathic FBS improved, and after use of Rikkosan for 1 week, she had days with no pain at all. Use of Rikkosan was continued for 1 month, with no worsening of the condition.

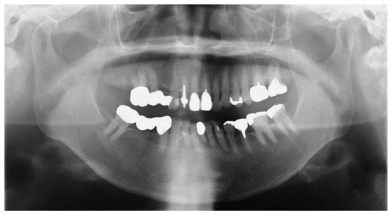

Fig. 1. Panoramic X-ray at the first examination. No dental focus of infection that could cause pain was found in the mandible.

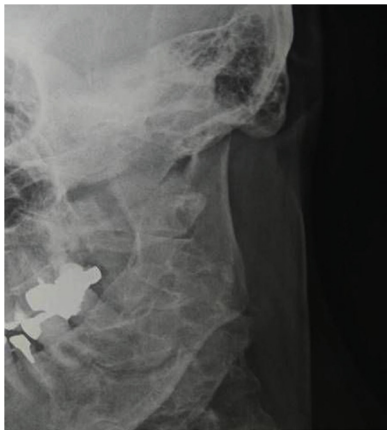

Fig. 2. X-ray taken at a tangent to the left parotid gland at the first examination. No salivary calculi were found in the left parotid region.

It was decided to temporarily discontinue use of Rikkosan in August 2016. However, there was an immediate recurrence of FBS. The patient was then instructed to dissolve approximately 0.5 g Rikkosan in 100 ml hot water, and as before, to hold the resulting mixture in the mouth for 30 s, gargle, and swallow it before meals. Although the Rikkosan was reduced from 1.0 g to 0.5 g, it was still effective for the pain. The patient reported either no symptoms at all or only mild discomfort. No drug-induced liver injury or allergy was found.

In October 2016, the patient was instructed to dissolve approximately 0.5 g Rikkosan in 100 ml hot water, to hold the resulting mixture in the mouth for 30 s, gargle, and then spit it out before meals. Even without swallowing Rikkosan, no aggravation of the FBS was observed during the clinical course.

In March 2017, gargling Rikkosan was discontinued, and the dietary strategy alone was continued, with no recurrence of FBS. The patient's anxiety regarding the pain on first bite improved, resulting in improved dietary quality of life.

As of this writing, there has been no recurrence of FBS for more than 2 years.

3. Discussion

The cardinal symptom of FBS is sharp pain in the parotid region, occasionally extending from the ear to the mandible, when taking the first bite at each meal; although the pain lasts for a few seconds, it gradually decreases and disappears with repeated mastication. However, the sharp pain occurs again at the first bite of the next meal. Patients become less inclined to eat because of the severe pain at every meal, which frequently results in reduced dietary quality of life [1,2,5].

The parotid gland is innervated by sympathetic and parasympathetic nerves that join at the otic ganglion and reach the parotid gland as the auriculotemporal nerve. Therefore, the parotid gland is under sympathetic and parasympathetic control, and the two systems together cause contraction of the myoepithelium of the parotid gland and regulate the quantity and characteristics of saliva secreted without antagonism [5,14,15]. The etiology of FBS is still unclear but the hypothesis of Netterville et al. [2] is currently considered the most plausible [2,5,11]. According to their hypothesis, loss of sympathetic nervous control of the parotid gland causes upregulation of receptors, resulting in denervation supersensitivity. As a result, there is a supranormal response to parasympathetic stimulation of the myoepithelial cells, and excessive contraction of these cells causes FBS. Kawashima et al. [4] reported that FBS occurs as a result of loss of sympathetic

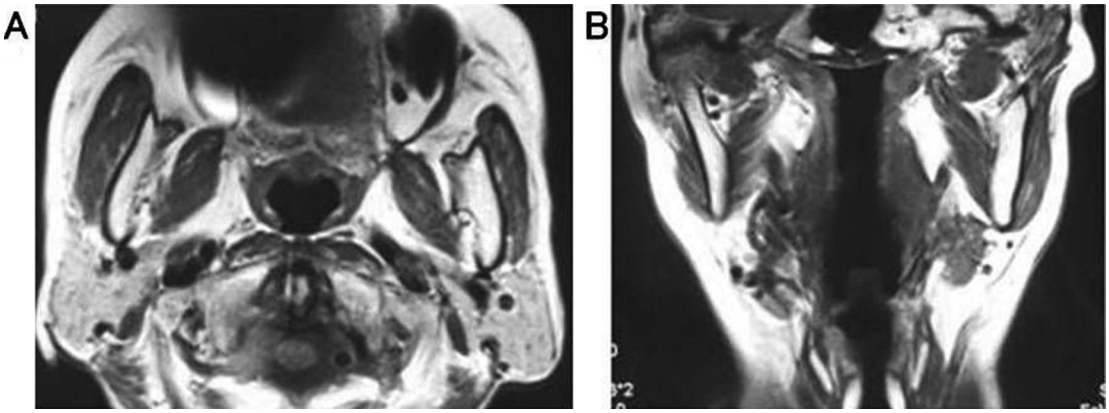

Fig. 3. Magnetic resonance imaging at the first examination. A horizontal T1-weighted image is shown on the left and a frontal T1-weighted image on the right. No structural changes were detected in the parotid glands, masseter muscle, parapharyngeal space, or neck region, and there were no findings of a tumor or inflammation.

innervation to the parotid gland from the superior cervical ganglion, and Komiyama et al. [4] considered FBS to be the result of a disorder of the sympathetic nervous system in the region between the superior cervical ganglion and sympathetic nerve plexus of the external carotid artery to immediately before the otic ganglion [16]. We thought that FBS involves changes in the composition of saliva over time. If the sympathetic nerves of the parotid gland are interrupted, viscous saliva with an increased amylase and protein content is produced as a result of the initial stimulus of eating food but cannot be readily secreted. Therefore, the pressure within the ducts increases, producing pain similar to salivary colic via the trigeminal nerve. If mastication continues, the amylase and protein content of the saliva gradually decreases, and there is also a decrease in the amount of saliva secreted as a result of the sympathetic nerve interruption, so that the pain decreases immediately

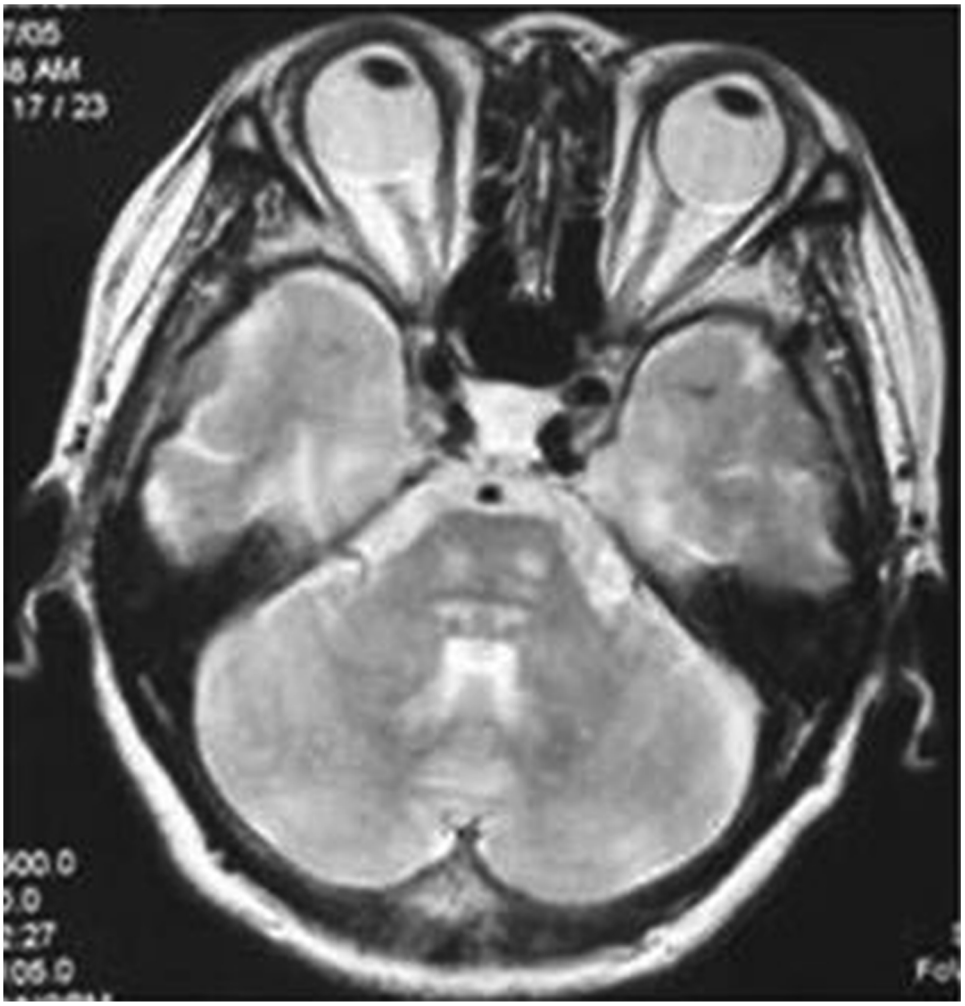

Fig. 4. Horizontal T1-weighted image of the head. No structural changes were found in the head and there were no findings of pressure on the trigeminal or glossopharyngeal nerve.

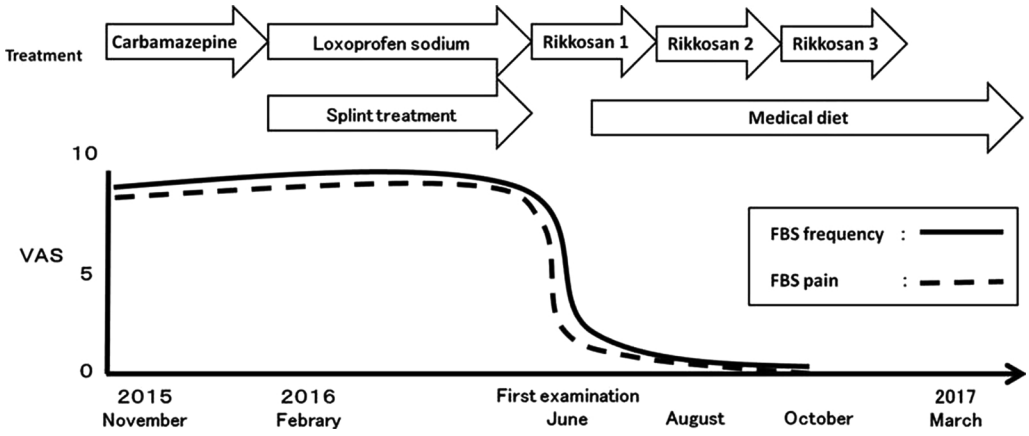

Fig. 5. Treatment and clinical course. Carbamazepine: 600 mg/day, orally. Loxoprofen sodium: 60 mg, as needed. Stabilization splint: use at night. Dietary strategy: First eat bitter and sweet foods, then eat salty and sour foods. Rikkosan 1: Approximately 1.0 g Rikkosan dissolved in 100 ml hot water, held in the mouth for 30 s, gargled, and swallowed before meals. Rikkosan 2: Approximately 0.5 g Rikkosan dissolved in 100 ml hot water, held in the mouth for 30 s, gargled, and swallowed before meals. Rikkosan 3: Approximately 0.5 g Rikkosan dissolved in 100 ml hot water, held in the mouth for 30 s, gargled, and spat out before meals. June 2016: Either no symptoms or only slight discomfort on Rikkosan 1. In addition, as a dietary strategy, the patient was instructed to first eat bitter and sweet foods, and then eat salty and sour foods. August 2016: immediate recurrence of symptoms when Rikkosan 1 was discontinued, and the patient was therefore restarted on Rikkosan 2. Either no symptoms or only slight discomfort. October 2016: change to Rikkosan 3, no aggravation of FBS. March 2017: Rikkosan 3 discontinued, dietary strategy continued. No recurrence of FBS at that time, and no subsequent recurrence of FBS. Abbreviations: FBS, first bite syndrome; VAS, visual analog scale score.

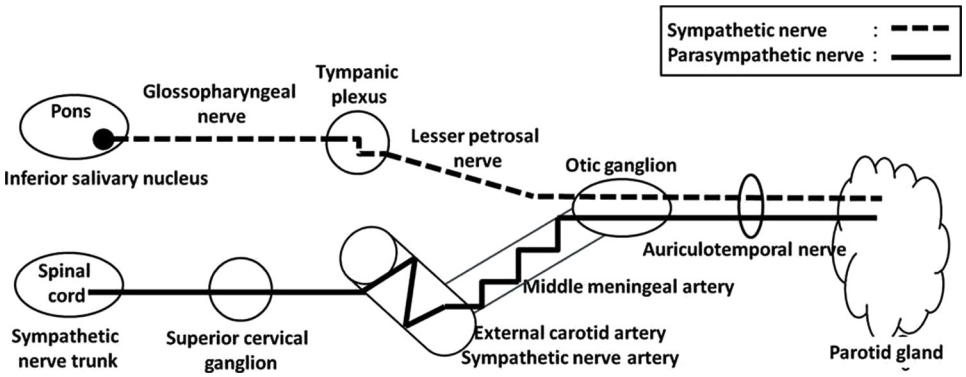

Fig. 6. Autonomic nervous control of the parotid gland. The sympathetic fibers innervating the parotid gland branch from the superior cervical ganglion and travel to the parotid gland along the middle meningeal artery after forming a plexus in the region of the external carotid artery. If sympathetic nervous control of the myoepithelial cells of the parotid gland is lost, the these cells become overstimulated in response to input from the parasympathetic nerve fibers as a result of denervation supersensitivity. The amylase and protein content of the saliva also increases during the initial stages of eating, and the saliva becomes viscous. As a result, the myoepithelial cells contract excessively, and viscous saliva is secreted in response to parasympathetic nerve excitation, thereby increasing the pressure in the parotid gland ducts, which causes pain.

[17]. Whatever the exact mechanism of onset, loss of sympathetic innervation appears to be involved (Fig. 6).

We thought that it is not clear whether FBS in patients with no history of possible nerve damage (idiopathic FBS [12,13]) and FBS in patients with a history of possible nerve damage (postoperative FBS) share the same etiological mechanism. Postoperative FBS [2] cannot explain the pathogenesis of idiopathic FBS, and there is little evidence that the sympathetic innervation of the parotid gland was affected in our patient. Furthermore, while gustatory stimuli-evoked facial pain has been reported previously [13], the idiopathic FBS in the present case differs from the gustatory stimuli-evoked pain described previously. Therefore, the pathogenesis of idiopathic FBS in the present case remains to be elucidated. Chiba et al. [13] reported that autonomic dysfunction impaired salivation in patients with diabetes and diabetic peripheral neuropathy, resulting in FBS.

Chiba et al. [13] devised the following diagnostic criteria for idiopathic FBS: (1) pain with the same characteristics as pain in postoperative FBS, that is, sharp pain that occurs in the parotid gland at the start of mastication at every meal and lessens as mastication continues; (2) sharp pain that occurs in the parotid gland when the tip of the tongue is stimulated with a sour taste; and (3) no history of surgery or tumors that might have injured the nerves of the parotid gland or parapharyngeal space, and other diseases causing pain in the parotid gland can be ruled out. In the present case, idiopathic FBS was diagnosed based on the characteristic clinical features of FBS and the exclusion of any other conditions in the differential diagnosis. There was no history of surgery, trauma, or radiation exposure to the head and neck. No salivary calculi were found on X-ray images. Tumor or inflammation of the jaw, parotid gland, masseter muscle, pharyngeal space, or neck was ruled out based on X-ray or MRI findings. Obstructive parotitis was also ruled out because gum test values were normal, MRI showed no obstruction of the major parotid gland ducts or segmental dilation, and no images showing abnormal salivary leak were found. In addition, trigeminal or glossopharyngeal nerve pain was excluded because there were no MRI findings of pressure on these nerves and the pain occurred with taste stimulation alone. A temporomandibular disorder was excluded because there was no local pain on motion and no specific trigger point in the mastication muscle group. Sialodochitis fibrinosa was also ruled out because there was no evacuation of solid deposits from the parotid gland ducts, white blood cell count was normal, and there were no MRI images showing constriction or irregular dilation of the parotid gland ducts. Fibromyalgia was also excluded because the attacks of pain were isolated, non-continuous, and short-lived, disappearing within a minute or so, and there was no chronic pain in any other part of the body. Furthermore, inflammatory changes were ruled out because the blood tests showed a normal white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate. Diabetic peripheral neuropathy was also ruled out because the fasting blood glucose was 105 mg/dl and the HbA1c (NGSP) was 5.7% (Fig. 7).

There have been several reports on treatment for FBS, but the effects are not always consistent, and with no treatment method yet

Differential diagnosis
Trauma
Salivary calculus
Parotitis
Parotid tumor
Masseteritis
Masseter muscle tumor
Trigeminal neuralgia
Glossopharyngeal neuralgia
Parapharyngeal space tumor
Sialodochitis fibrinosa
Temporomandibular disorder
Fibromyalgia

Fig. 7. Differential diagnosis of first bite syndrome.

Treatment methods
Medical diet
Pharmacotherapy
・Carbamazepine
・Gabapentin
・Atropine sulfate
・Amitriptyline
・NSAID s
・Goreisan
・Rikkosan
Nerve block
・Stellar ganglion block
Surgical treatment
・Auriculotemporal nerve resection
・Tympanic plexus resection
Botulinum toxin therapy
Radiotherapy

Fig. 8. Treatment of first bite syndrome. NSAIDs, nonsteroidal anti-inflammatory drugs.

established, addressing the condition has become a source of difficulty [2,3,5,6,10,11,13] (Fig. 8). Injection of botulinum toxin into the parotid gland for FBS has recently yielded extremely promising results for what was regarded as an intractable disease. However, the safety of botulinum toxin and the long-term prognosis remain to be seen [18–20]. In the present case, we conjecture that gargling Rikkosan before eating caused secretion of saliva in response to taste stimuli that were weaker than sour or salty stimuli and that the local anesthetic properties of Rikkosan also suppressed taste stimulation. Therefore, the excitement of the parasympathetic system from stimulation of the gustatory-salivary reflex at the start of eating was suppressed, such that both excessive contraction of the myoepithelium of the parotid gland and excessive salivation were suppressed. Thus, a sudden increase in pressure within the parotid gland ducts was avoided, preventing the onset of pain (Fig. 9). FBS has been reported to be readily induced by sour tastes in particular [1,2,5], and it appears that the instruction to eat bitter and sweet foods first and salty and sour foods second as a dietary strategy [2] to suppress the secretion of saliva via the gustatory-salivary reflex at the first bite also contributed to improvement of the FBS in our patient.

Rikkosan is a type of traditional Chinese medicine (*kampo*) that contains five major ingredients: *kanzo* (Glycyrrhiza), *shoma* (Cimicifuga rhizome), *ryutan* (Japanese gentian), *saishin* (Asiasarum root), and *bofu* (Saposhnikovia root). Rikkosan has been widely used to treat orofacial pain and has been shown to be effective in the treatment of trigeminal neuralgia, glossopharyngeal neuralgia, toothache, gingival pain, tooth extraction pain, mouth ulcers, and glossalgia. Saishin, one of the main components, contains capsaicin, which has a pungent sharp taste and acts as a local anesthetic by depleting substance P. We conjectured that, in the present case, gargling Rikkosan before a meal reduced taste stimulation on eating via the bitter taste and local anesthetic action of Rikkosan. This effect reduced the secretion of saliva so that the pressure increase in the parotid gland ducts was suppressed, so FBS did not occur. Chiba et al. [13] also reported the usefulness of Rikkosan taken before meals, and this is believed to be because secretion of saliva at the start of mastication was reduced as a result of the salivation caused by the bitter taste of Rikkosan before eating. Rikkosan was also efficacious in the present case, and while its exact mode of action remains speculative, the dramatic improvement in the patient's FBS suggests that Rikkosan should be the first treatment attempted for this condition.

There are still few published reports on the clinical course of FBS, which appears to vary from patient to patient. Therefore, there is still no clear explanation of the mechanism of onset, the natural course of the condition, or its treatment. In this case, improvement in idiopathic FBS occurred as a result of gargling and then swallowing Rikkosan. However, the mechanism of onset of idiopathic FBS and the mechanism of the effective action of Rikkosan remain unclear, and the outcomes in further cases are awaited.

Ethics approval

Since there is no information that can identify individuals in this paper, approval by the ethics committee is unnecessary. Fully informed consent was obtained from the patient for the use of clinical information relating to this case.

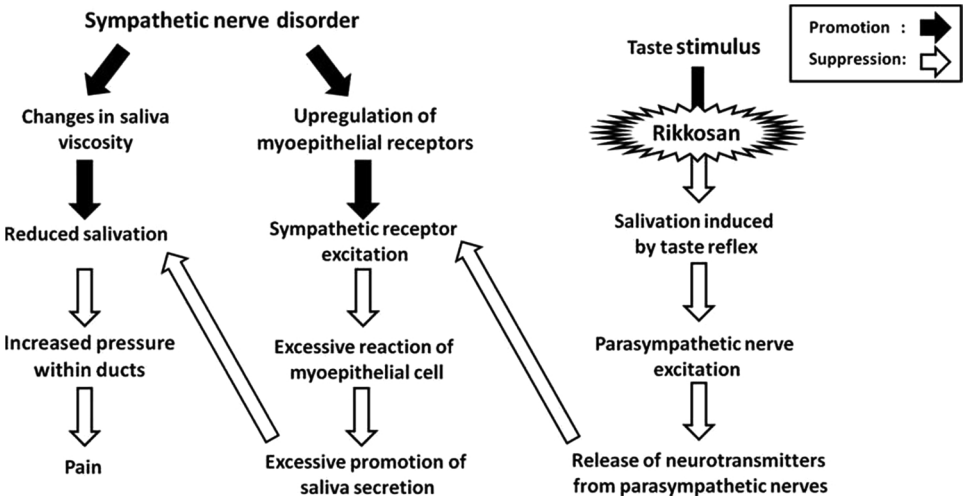

Fig. 9. Mechanism of action of Rikkosan in first bite syndrome. Holding Rikkosan in the mouth before eating causes taste stimuli that are weaker than sour or salty food and the local anesthetic action of Rikkosan also suppresses taste stimulation, thereby suppressing excitement of the parasympathetic nervous system by stimulation of the gustatory-salivary reflex. The result is that both excessive contraction of the myoepithelium in the parotid gland and excessive salivation are suppressed, so that a sudden increase in pressure within the parotid gland ducts is avoided, and the pain is suppressed.

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of interest

The authors declare that they have no competing interests.

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