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Original Article

Ear, Nose and Throat Section

Diagnostic Utility of Infratemporal Fossa Sign in Patients with Laryngeal and Oesophageal Reflux Diseases: A Prospective Observational Study

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ABSTRACT

Introduction: The Infratemporal Fossa (ITF) sign is defined as the patient's localisation of pain to the posterior infra-auricular or retromandibular area. This pain is attributed to oedema of the pharyngeal end of the Eustachian Tube (ET), which can be observed using Diagnostic Nasal Endoscopy (DNE). Reflux disease is one of the various causes of ET salpingitis.

Aim: To determine the incidence of the ITF sign in patients with Laryngopharyngeal Reflux (LPR) and to identify the percentage of patients presenting with the sign who also have underlying LPR.

Materials and Methods: This prospective observational study was conducted at a tertiary care centre in the Department of Ear, Nose and Throat (ENT) and General Surgery at Karuna Medical College, Palakkad, Kerala, India from February 2024 to July 2024. Patients exhibiting the ITF sign, as well as those diagnosed with gastroesophageal conditions who also presented with the ITF sign, were evaluated for the presence of LPR using the Reflux Symptom Index (RSI). DNE and video laryngoscopy were performed, and the medial ET changes and LPR changes were graded using the 3ET score and Reflux Finding Score (RFS), respectively, in all patients with the ITF sign. Patients underwent a six-week course of Proton Pump Inhibitor (PPI) therapy and were subsequently re-evaluated using the RFS and 3ET score. The pre- and post-treatment scores were statistically analysed using a paired t-test.

Results: A total of 68 patients were included. Of these, 47 presented with the ITF sign as their initial complaint, and 21 patients with Gastroesophageal Reflux Disease (GERD) also displayed the ITF sign. The mean RFS value was 15.15 before treatment, and after six weeks of PPI treatment, the mean value was 6.66. The mean 3ET DNE scores were 4.47 and 1.82 before and after treatment, respectively.

Conclusion: The ITF sign can be considered one of the indicators of LPR disease.

Keywords: Eustachian tube, Laryngopharyngeal reflux, Proton pump inhibitors

INTRODUCTION

The GERD is defined as the retrograde flow of stomach acid secretions into the oesophagus. This backflow is primarily caused by postprandial transient relaxation of the lower esophageal sphincter and decreased sphincteric pressure [1]. In contrast, LPR, often considered an Extra Oesophageal (EE) manifestation of GERD, occurs when retrograde stomach contents travel up to the mucosa of the upper aerodigestive tract [2]. Despite the differences in symptoms between GERD and LPR, both conditions share similar underlying physiological mechanisms, and their treatment approaches are also quite similar [3,4].

The GERD typically presents with symptoms such as dysphagia, heartburn, and upper abdominal discomfort, often described as a feeling of bloating after eating. In contrast, LPR presents with non specific symptoms such as frequent throat clearing, persistent non-productive coughing, changes in voice, and a sensation of a lump in the throat. LPR can occur without the typical symptoms of GERD, a condition sometimes referred to as silent GERD. Owing to its subtle presentation, LPR is often diagnosed very late. Both LPR and GERD can cause reflux-induced inflammation of the medial end of the ET, which may lead to ear discomfort [5,6].

Diagnosing reflux diseases in patients presenting with non specific symptoms poses a significant challenge for clinicians. The gold standard for diagnosing reflux disorders is 24-hour multiprobe pH monitoring combined with sphincteric pressure measurement using manometry [7]. In addition, the RSI, a subjective questionnaire, and the RFS, assessed using a videolaryngoscopic examination, are valuable, validated clinical tools for diagnosing LPR [8,9].

One of the many non specific symptoms is the localisation of pain in the retromandibular/posterior infra-auricular area, known as the ITF sign [10]. This symptom is attributed to edema at the pharyngeal end of the ET, which can be visualised through nasal endoscopic examination.

The objectives of present study were to evaluate the incidence of the ITF sign in patients with LPR and to assess the effectiveness of treatment in alleviating the ITF sign. To the best of our knowledge, this is the first study of its kind aimed at establishing a relationship between the ITF sign and reflux diseases.

MATERIALS AND METHODS

A prospective observational study was conducted from February 2024 to July 2024 in the Department of ENT and General Surgery at Karuna Medical College, Palakkad, Kerala, India. Clearance from the Institutional Ethics Committee (IRB No: KMC/IHEC/08/2024) was obtained. Patients who presented with the ITF sign in the ENT Outpatient Department (OPD) were evaluated for LPR/GERD. Similarly, patients presenting with GERD/LPR symptoms in the surgery outpatient department (assessed using the RSI and RFS) were asked about the presence of the ITF sign.

Sample size calculation: With the incidence of LPR reported as 5% [11], a confidence interval of 95%, and a margin of error of 5%, the recommended minimum sample size (n) required was 60.

Inclusion criteria: Patients who were older than 18 years of age; those willing to provide written informed consent for participation; those presenting with pain behind and below the pinna (suggestive of the ITF sign); and those diagnosed with LPR, GERD, or both, with a positive ITF sign were included.

Exclusion criteria: Patients with a deviated nasal septum; allergic rhinitis; chronic rhinosinusitis; comorbidities such as diabetes mellitus, hypothyroidism, or neurological diseases; a recent history of surgical procedures involving the nasal/nasopharyngeal area or upper digestive tract; recent otitis media, pharyngitis, or respiratory tract infections; signs of ET dysfunction observed during otoendoscopic examination or tympanometry; and tympanic membrane perforation observed on otoendoscopy were excluded.

Study Procedure

The RSI is a subjective questionnaire containing nine questions that assess the severity of symptoms associated with LPR, with a score of 13 out of 45 considered abnormal and suggestive of LPR [12]. For patients with an RSI score greater than 13, a laryngeal examination was conducted using a 70-degree Hopkins rod endoscope. The findings from this examination were graded using the RFS, an objective tool where a score above seven indicated a 95% probability of LPR [13]. A case of LPR was defined as a patient with RSI and RFS values exceeding 13 and seven, respectively.

The diagnosis of GERD was based on a thorough history that included inquiries about heartburn, retrosternal discomfort, and regurgitation. Flexible upper oesophagogastroduodenoscopy was also performed to rule out erosive or other pathological causes of GERD symptoms. Patients with abnormal endoscopic findings in the oesophagus or stomach were excluded from the study and advised to undergo further evaluation.

Once the ITF sign was identified, a Direct Nasal Endoscopy (DNE) was performed to check for inflammation at the medial end of the ET. The DNE was conducted under local anaesthesia, with the nasal cavity anaesthetised using cotton wicks soaked in xylometazoline hydrochloride nasal solution (0.05%) and lignocaine (4%) topical preparation in a 1:1 ratio for 10 minutes. A zero-degree Hopkins rod nasal endoscope was used to perform the Direct Nasal Endoscopy (DNE). The changes at the medial end of the ET orifice were graded according to the 3ET grading system proposed by McCoul ED et al., [14]. The 3ET score evaluates the presence of edema, erythema, and exudates at the medial end of the ET, along with hypertrophy of the tubal tonsil. Each parameter is assigned a score of 0, 1, or 2 according to its severity as observed during the DNE.

An otoendoscopic examination and tympanometry were also performed for patients experiencing pain below and behind the pinna to rule out any middle ear pathology that could contribute to the retroauricular pain.

Patients with the ITF sign who did not exhibit characteristic endoscopic changes were categorised separately and kept under follow-up. Those with the ITF sign and positive endoscopic findings were provided with standard treatment consisting of oral pantoprazole, a Proton Pump Inhibitor (PPI), for six weeks. A dosage of 40 mg twice daily of pantoprazole for all the patients. After this period, the presence of the ITF sign was reassessed, and patients willing to undergo another endoscopic examination were re-evaluated and graded accordingly. Patients who did not respond to PPI therapy were subjected to further evaluation to rule out any other underlying pathology contributing to their symptoms.

STATISTICAL ANALYSIS

The data were tabulated and analysed using Statistical Package for Social Sciences (SPSS) version 28.0 (IBM, Armonk, NY, USA). A Shapiro-Wilk test was performed to confirm whether the present data followed a normal distribution, and it was found that the data were normally distributed. A paired t-test was conducted to compare the pre- and post-treatment values of the RSI, RFS, and 3ET scores.

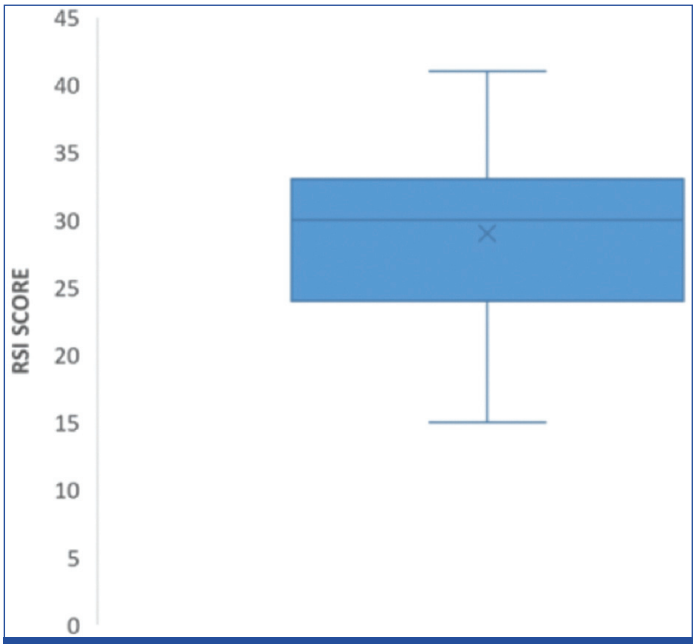
RESULTS

A total of 68 patients were included in the study, with 30 being male, resulting in a male-to-female ratio of 1:1.26. During the study period, 47 patients presented with pain in the retroauricular area, which was diagnosed as the ITF sign. Additionally, 21 out of 82 patients who presented to the surgery OPD with symptoms suggestive of GERD reported having a positive ITF sign when asked the leading question, "Do you experience intermittent pain behind the ear?" Most of the patients were aged between 25 and 50 years, with a mean age of 43.79 years [Table/Fig-1].

Parameters	n (%)
Age distribution	
25-40 years	24 (35.3%)
41-50 years	24 (35.3%)
51-63 years	20 (29.4%)
Mean±SD age (in years)	43.79±9.79
Gender	
Male	30 (44.1%)
Female	38 (55.9%)

[Table/Fig-1]: Showing age and gender details of the patients.

All patients who were diagnosed with a positive ITF sign (n=68) were asked to complete the RSI questionnaire before beginning treatment for reflux disease. Upon analysing the data, it was found that patients with the ITF sign had an RSI score greater than 13. The mean RSI score was 28.98, with a standard deviation of 5.96 [Table/Fig-2].

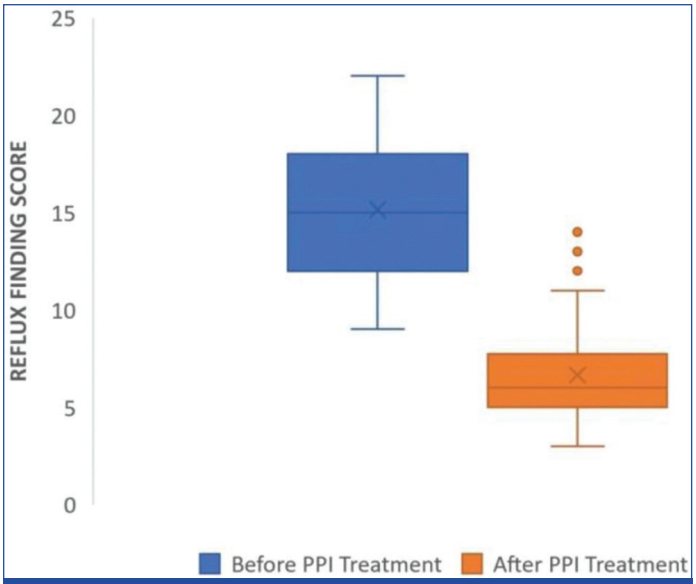


[Table/Fig-2]: Showing reflux symptom index score in study population.
RSI: Reflux symptom index

A standard treatment protocol was prescribed for all patients, and the incidence of the ITF sign was re-evaluated after treatment. Seven patients continued to exhibit the ITF sign even after completing the treatment. Only two of these patients had initially presented with the ITF sign as their primary complaint.

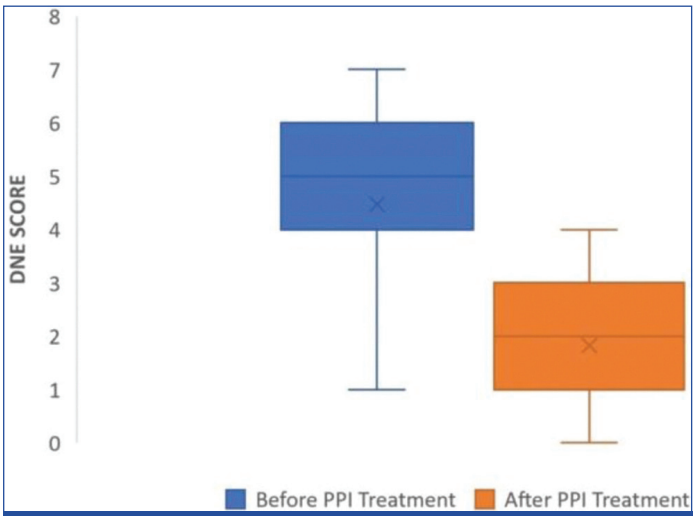
The mean RFS before the initiation of PPI treatment was 15.15. Among patients who presented with the ITF sign, the mean RFS was 15.38, while for those presenting with reflux symptoms, it was 15.19. After six weeks of PPI treatment, the mean RFS value decreased to 6.66, with a mean difference of 8.49. The mean RFS value was higher among patients who no longer had the ITF sign (mean RFS=6.61, n=61) compared to those who continued to have a positive ITF sign (mean RFS=5.79, n=7). However, a paired t-test showed that the reduction in RFS values after treatment was statistically significant, with a p-value of <0.0001 [Table/Fig-3].

A significant reduction in the 3ET scores was observed after six weeks of PPI therapy compared to pretreatment values [Table/



[Table/Fig-3]: Showing pre and post-treatment Reflux Finding Score (RFS) mean values.
PPI: Proton pump inhibitor

Fig-4]. Before the initiation of therapy, the mean 3ET score was higher among patients who presented with reflux symptoms (4.46±1.45) compared to those who presented with the ITF sign as the first symptom (4.36±1.40). However, the difference in mean values was not statistically significant (p-value using Student's t-test=0.09). The majority of patients had a 3ET score of 4 or higher before treatment initiation 53 (77.9%) [Table/Fig-5]. Patients who continued to exhibit the ITF sign after treatment had a mean 3ET score of 1.88, which was slightly higher than the mean score of 1.82 among those who no longer showed the ITF sign after treatment [Table/Fig-6]. To summarise, there was a noticeable difference in the mean values when comparing the pretreatment and post-treatment values, with a mean difference of 8.49 for RFS and 2.64 for the 3ET score [Table/Fig-7].



[Table/Fig-4]: Showing pre and post-treatment 3ET DNE score.
DNE: Diagnostic nasal endoscopy; PPI: Proton pump inhibitor

Total 3ET score	Pre-treatment		Total number of patients N (%)
	Number of patients with ITF* sign as presenting complaint n (%)	Number of GERD† patients with ITF* sign n (%)	
1	1 (2.13%)	1 (4.76%)	2 (2.94%)
2	5 (10.64%)	1 (4.76%)	6 (8.82%)
3	6 (12.76%)	1 (4.76%)	7 (10.29%)
4	11 (23.40%)	5 (23.82%)	16 (23.53%)
5	13(27.66%)	6 (28.57%)	19 (27.94%)
6	10 (21.28%)	6 (28.57%)	16 (23.53%)
7	1 (2.13%)	1 (4.76%)	2 (2.94%)
Total number of patients	47 (100%)	21 (100%)	68 (100%)
3ET DNE‡ Mean±SD§	4.36±1.40	4.46±1.45	4.47±1.41

[Table/Fig-5]: Distribution of the pretreatment 3ET DNE scores of the patients.
*ITF Sign: Infratemporal fossa sign; †GERD: Gastroesophageal reflux disease; ‡DNE: Diagnostic nasal endoscopy; §SD: Standard deviation

Total 3ET score	Post-treatment		Total number of patients N (%)
	Number of patients with ITF* sign positive n (%)	Number of patients with ITF* sign negative n (%)	
0	0	7 (11.48%)	7 (10.29 %)
1	4 (57.14%)	15 (24.59%)	19 (27.94%)
2	0	21 (34.43%)	21 (30.88%)
3	2 (28.57%)	12 (19.67%)	14 (20.59%)
4	1 (14.29%)	6 (9.83%)	7 (10.29%)
5	0	0	0
6	0	0	0
7	0	0	0
Total number of patients	7 (100%)	61 (100%)	68 (100%)
3ET DNE† Mean±SD‡	1.88±1.29	1.82±1.10	1.83±1.11

[Table/Fig-6]: Distribution of post-treatment 3ET DNE scores.
*ITF Sign: Infratemporal fossa sign; †DNE: Diagnostic nasal endoscopy; ‡SD: Standard deviation

Parameters	Pretreatment	Post-treatment	Difference in mean value±SD	p-value*
RFS†-Mean±SD‡	15.15±3.73	6.66±2.48	8.49±1.25	<0.0001
3ET score Mean±SD‡	4.47±1.42	1..82±1.12	2.65±0.30	<0.0001

[Table/Fig-7]: Comparison of RFS and 3ET scores.
*In paired test, p-value considered as statistically significant if p<0.05, †RFS: Reflux finding score; ‡SD: Standard deviation

DISCUSSION

The GERD is a common gastrointestinal disorder characterised by the retrograde flow of stomach contents into the oesophagus [15]. These contents typically include a mixture of acidic stomach secretions and alkaline fluids from the duodenum and pancreas, which can enter the oesophagus [16]. Several mechanisms contribute to this process, including impairment of the lower esophageal sphincter due to repeated transient lower esophageal sphincter relaxation, the presence of a hiatal hernia, impairment of the oesophageal mucosal barrier, and abnormalities in esophageal peristalsis [17]. In some cases, the refluxate can enter sites beyond the oesophagus, leading to symptoms collectively termed extraesophageal GERD [18].

Various theories have been proposed to explain the pathogenesis of extraesophageal gastroesophageal reflux disease (EE GERD). Kaufmann introduced the term Laryngopharyngeal Reflux Disease (LRD), which can be considered a variant of EE GERD that occurs when the backflow of gastric contents reaches the upper aerodigestive tract [19]. LPRD may result from defective upper esophageal sphincter and mucosal barrier mechanisms. Normally, the upper and lower esophageal sphincters remain in a tonic-contracted state, relaxing only during swallowing or coughing. A defective sphincter mechanism allows the refluxate to enter the upper airway tract [20].

The pathophysiology of GERD differs from that of LPR in certain aspects. The laryngeal mucosa is composed of delicate squamous

and respiratory-type epithelium, whereas the lower oesophagus is lined with columnar epithelium. Once the refluxate reaches the larynx, it cannot be removed by peristalsis or neutralised by bicarbonate secretions, as it can in the lower oesophagus [21]. The primary agent responsible for damaging the laryngeal mucosa is pepsin, which is the active form of the zymogen pepsinogen. The conformational changes that occur at the molecular level influence the effect of pepsin on the mucosal surface. Pepsin has optimal activity at a pH of 2, and in the pH range of 4-6.5, pepsin undergoes structural changes and reaches an intermediate conformation. The protease activity of this aspartate-containing molecule is absent in this pH range; however, the molecule can undergo reverse conformation when the pH becomes acidic within 24 hours. Therefore, the inactive pepsin in the upper aerodigestive mucosa can be reactivated when refluxate with an acidic pH ascends higher in the oesophagus [22].

In other words, pepsin can remain active in environments with a pH as high as seven and can cause irreversible damage when the pH exceeds eight [23].

In the laryngeal region, pepsin is mainly observed in fine aerosol or droplet form, in contrast to the liquid form found in the lower oesophagus. This aerosolised pepsin can reach the nose, nasopharynx, oropharynx, and even the oral cavity [24]. The time required for pepsin to cause mucosal damage is minimal, as just 30 seconds of contact, three times per week, is sufficient to cause symptoms of LPR [19]. In a study by Formánek M et al., the results of 24-hour multichannel intraluminal impedance-dual-channel pH monitoring were compared with the estimation of pepsin in the laryngeal mucosa. They found that the detection of pepsin by immunohistochemistry was positive in patients with six or more pharyngeal refluxes [25]. Thus, it is evident that a shorter duration of contact and a few reflux episodes are enough for pepsin to cause laryngeal mucosal changes [19,25].

The pepsin-mucosa interaction can activate several pro-inflammatory pathways and alter mucous composition [26]. This is supported by the fact that pepsin levels are significantly high in mucous secretions from patients with otitis media with effusion and LPR. A low pH in the upper aerodigestive tract is known to trigger the reflux mechanism via the vagus nerve, leading to increased mucus secretion [27]. This may explain the incidence of serous otitis media and dry mouth in patients with LPR [28]. Another important chemical in the refluxate that can cause mucosal damage is unconjugated bile acids [29].

The main symptoms of LPR include hoarseness of voice, frequent throat clearing, postnasal drip, coughing, episodes of breathing difficulty or choking after a heavy meal or while lying down, and a sensation of a foreign body lodged in the throat [30]. The refluxate can travel up into the oropharynx, causing chronic tonsillitis, or into the nasopharynx, causing nasopharyngitis [31]. One of the important structures in the nasopharynx is the medial orifice of the Eustachian tube (ET). Inflammation in this area can lead to Eustachian tube salpingitis (ES), which presents with symptoms that are often uncharacteristic and confusing. The ITF sign may be an indicator of underlying chronic ES [32]. Close differential diagnoses for ES-related pain localised in and around the ear include temporomandibular joint arthralgia and middle ear pathology [33]. A study by Parsel SM et al., showed that in patients with ES, the localisation of pain to the ITF area was significant [32].

The exact incidence of nasopharyngeal reflux is unclear. However, many studies have highlighted its association with chronic rhinosinusitis, recalcitrant allergic rhinitis, and serous otitis media, especially in children [34-39]. In addition, the occurrence of Barrett's oesophagus was found to be higher in patients with nasopharyngeal reflux disease, further establishing the connection between chronic GERD and the occurrence of Extraesophageal GERD (EE GERD) [40].

In patients with the ITF sign, the localisation of pain specifically to the inferior aspect of the root of the pinna may be attributable to several factors. The authors propose the following mechanisms and encourage further research in this area: i) the medial orifice of the ET and the ITF sign area lie in the same horizontal plane; ii) referred pain mediated by the branches of the trigeminal nerve; iii) communication between the fibers of the glossopharyngeal nerve and the vagus nerve; and iv) vagus nerve-mediated neural pain. The nasopharyngeal mucosa is innervated anteriorly to the ET orifice by the branches of the maxillary nerve and posteriorly by the glossopharyngeal nerve [41].

Another branch of the trigeminal nerve, the mandibular nerve, is the chief component of the neurovascular bundle in the Infratemporal Fossa (ITF) [42]. The glossopharyngeal nerve occasionally gives off a communicating branch to the vagus nerve. Some patients with glossopharyngeal neuralgia have been found to experience excessive vagal stimulation during attacks. This neural cross-connection could also be a potential cause of the ITF sign, as the root of the pinna is innervated by branches of the vagus nerve [43]. Additionally, the reflux mechanism is known to activate neural pathways associated with the vagus nerve [44]. These interconnected neuronal links may contribute to the localisation of pain characteristic of the ITF sign.

Nasopharyngeal reflux, like LPR, is often a silent reflux, as it is underdiagnosed in most cases. The present study demonstrated that in patients with the ITF sign and reflux disease, treatment with proton pump inhibitors (PPIs) can alleviate nasopharyngitis, as 61 out of 68 patients reported the absence of the ITF sign after treatment. It is important to differentiate between ET dysfunction and Eustachian tube Salpingitis (ES), as the former requires prompt medical and surgical treatment.

Limitation(s)

The limitations of present study include the inability to detect or measure the presence of pepsin in the nasopharynx, as well as the lack of pH estimation for the exudates at the ET orifice, and the esophageal and laryngeal mucosa.

CONCLUSION(S)

The ITF sign can be considered one of the symptoms of LPRD. A thorough evaluation of the laryngeal and esophageal areas is important to determine the underlying cause of the ITF sign. In patients with ITF signs and gastroesophageal reflux or LPRD, treatment with PPIs may effectively cure ES.

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