Extra-laryngeal manifestations of gastro-oesophageal reflux

Manifestazioni extralaringee della patologia da reflusso gastroesofageo

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Summary

Of the various otorhinolaryngological disorders for which it has been recognized that gastro-oesophageal reflux is a possible causal or associated aetiological factor, those manifestations localized in the rhino-sinus and auricular district are certainly the "least studied". Herein, therefore, these manifestations are described, focusing on the physio-pathological aspects and the more important pathogenic hypotheses of the cough, as well as other lung manifestations.

Riassunto

Tra tutte le patologie otorinolaringoiatriche che riconoscono nel GER il possibile fattore eziologico causale o concausale, le manifestazioni a carico del distretto rinosinusale e auricolare sono sicuramente quelle "meno studiate". Vengono pertanto presentati gli aspetti fisiopatologici di queste manifestazioni e le ipotesi patogetiche più rilevanti della tosse così come delle altre manifestazioni polmonari.

The first mention of otorhinolaryngological disorders being correlated with gastro-oesophageal reflux (GER) dates back to the early part of the 20th Century – 1903, when Coffin hypothesized that the "reflux of gas from the stomach" and "hyperacidity" were responsible for laryngeal and nasal symptoms in patients presenting hoarseness and posterior rhinorrhea. Since then, other Authors have indicated reflux as a possible cause of laryngomalacia, subglottic stenosis, laryngospasm, reflex apnoea, bronchoconstriction, otitis and rhinosinusitis [1-4].

Since the eighties, alongside the relatively "old" knowledge of GER, a new concept has been born, namely pharyngo-laryngeal reflux (LPR) referring to the part of the acid refluxate material from the stomach which, besides coming into contact with the oesophageal mucosa, after having crossed also the upper oesophageal sphincter (UES), comes into contact with the anatomic structures of the upper and lower respiratory pathways: larynx, hypopharynx, tracheo-bronchial tract, sometimes even reaching the rhinosinusal and auricular areas [3 5 6].

It has become increasing clear, over the last few years, that patients with GER are considerably different from those with LPR on account of various characteristics: physio-pathological mechanism, mode of presentation, symptoms and response to medical treatment or surgery [7].

The physio-pathological mechanism basically responsible for GER is LES dysfunction and dysmotility of the oesophageal body; on the contrary, in patients with LPR, oesophageal motility is good whereas UES function is poor. Thus, while in patients with GER, the predominant symptom is pyrosis and/or regurgitation, the symptoms in patients with LPR depend upon the anatomical structures involved in the acid reflux such as dysphonia, feeling of pharyngeal globus, cough, hoarseness, posterior rhinorrhea with intermittent nasal obstruction and feeling of auricular obstruction and disorders in the oral cavity. In these patients, these symptoms, are unlikely to be found together with pyrosis, dyspepsia, belching and regurgitation [8].

For this reason, patients with GERD present a "*typical*" symptomatology since it is related to the insult of the acid reflux on the oesophageal mucosa, while that of LPR presents co-called "*atypical*" symptoms since, according to a somewhat antiquated, and now outdated theory, expression of an insult on areas not reached by the refluxate. As a result of this clear symptomatological division, it has been defined as a "*silent*" LPR, almost as if to stress the absence, in these patients, of typical symptoms [5].

Thus as for the symptoms, also the more common clinical manifestations of gastro-oesophageal or laryngo-pharyngeal reflux are different and represented, respectively, by oesophagitis and posterior laryngitis [7].

Albeit, the fact that, with time, two very different categories of patients have emerged should not result in neglecting the concept of gastro-oesophageal reflux as a sole physio-pathological factor that may present with "typical" or "atypical" symptoms, depending upon the anatomical districts involved, but which, sometimes, appear in the same individual with both symptoms simultaneously.

Of the various otorhino-laryngological disorders for which it has been recognized that GER is a possible causal or associated aetiological factor, those manifestations localized in the rhino-sinus and auricular district are certainly the "least studied".

The fact that these attract less attention than laryngo-pharyngeal disorders due to gastro-oesophageal reflux, stems from two different aspects. On the one hand, only over the last ten years have Authors broadened their perpectives and considered gastro-oesophageal reflux as being potentially responsible, both in the adult and paediatric population, either alone or in association with other associated factors, particularly of those chronic rhino-sinusal and auricular inflammatory processes resistant to common medical treatment. On the other hand, the almost total lack of studies including a control group demonstrating the presence of acid material at nasal cavity, paranasal and middle ear level, albeit a condition which is difficult to demonstrate on account of the extreme difficulty in assessing the pH in those anatomical areas under consideration, thus leaving some doubt and certainly making it difficult to confirm the hypothesis that gastro-oesophageal reflux is one of the factors, or the exclusive factor, responsible for the onset of otorhino-laryngological disorders.

Auricular manifestations, particularly otitis media with effusion, are found almost exclusively in the neonatal and infantile age groups [9-11].

The reason for this assumption lies in the fact that tubaric dysfunction is more frequent in children than in adults. There are numerous factors predisposing to this condition which are related to the anatomical differences between adults and children as far as concerns the Eustachian tube, the greater likelihood of catching the more common infections of the upper respiratory airways, as well as the congenital and acquired impairments in ciliary movement. Only recently has oesophago-laryngo-pharyngeal reflux been taken into consideration [12], as a possible risk factor for tubaric dysfunction.

This is why reflux, in the neonatal period, could be held to be the major event triggering secretory otitis media and there are two reasons, which are only apparently negligible, but which would account for this: the number of reflux episodes is greater than in adults and the supine position is maintained throughout almost the entire day. The pathogenetic mechanism responsible for secretory otitis media, in chil-

dren with associated laryngo-pharyngeal reflux, is related to the contact of the refluxate with the rhino-pharyngeal areas and, consequently, with the pharyngeal orifice of the Eustachian tube. Repeated exposure of the ciliated epithelium of the respiratory tract to a pH of 4 or less, inevitably leads to stasis of the latter. In turn, this results in impaired mucociliar clearance. Furthermore, hydrochloric acid and pepsin induce local inflammation, mucosal oedema and ulcerations in the mucosa of the respiratory tract; inflammation of the Eustachian tube, in particular, causes an obstruction which, in turn, leads to loss of ventilatory function. This damage triggers a series of events leading to an objective otoscopic pattern of effusive otitis media [13].

The only doubt, until a few years ago, was whether or not the acid reflux entered the tympanum, thus damaging, not only directly but also indirectly, the mucosa of the middle ear, or whether the damage was limited only to the mucosa of the Eustachian tube.

A reply to this enigma emerged from the results of a study performed on specimens of the secretion from the middle ear of small patients submitted to bilateral paracentesis tympanum due to secretory otitis media. From an analysis of this liquid, it was found that 91% of the specimens demonstrated an acid pH with high concentrations of pepsin and pepsinogen, thus confirming the theory that laryngo-pharyngeal reflux could represent an interesting risk factor for secretory otitis media [14].

Also the naso-sinusal, not unlike auricular manifestations, are more frequent in paediatric age, presenting as chronic inflammatory processes in the nasal and paranasal cavities. The pathogenetic mechanism by means of which the acid refluxate involves the nose and paranasal sinuses remains to be elucidated.

In the past, two possible mechanisms have been proposed. The first refers to a direct action of the hydrochloric acid and the pepsin upon the respiratory mucosa in the nasal and sinus areas, as previously described in the auricular district. Thus having excluded the hypothesis that the refluxate material could directly reach the paranasal sinuses passing through the ostium, it was then hypothesized that it was more likely that the gastric reflux reached the rhino-pharyngeal area and the posterior part of the nasal cavity where only the ostium of the sphenoidal sinus is present. Thus, the acidity could induce inflammation of the nasal mucosa leading to oedema and, therefore, obstruction of the ostio-meatal complex [15 16].

The second mechanism proposed refers to a reflex arch, as hypothesized at laryngeal level, characterized by hyperreactivity of the autonomous nervous system induced by the refluxate material which would then cause nasal oedema leading to obstruction of the ostium of the paranasal sinuses [17]. Albeit,

all the studies carried out so far, despite having demonstrated the presence of oesophago-laryngo-pharyngeal reflux in paediatric patients with chronic rhino-sinusitis, not responding to conventional medical treatment, failed to demonstrate a direct causal relationship between the two conditions [18].

Furthermore, over the last few years, increasing attention has been focused on the possibility that the cough, a highly aspecific symptom and possibly related to various pathological conditions, especially when "chronic", i.e., persistent for a period of more than 8 weeks, and non-responsive to the most frequently used medical drugs, could even be the first and only symptomatological manifestation in patients with GER [19] [20].

Irwin, of all the research workers who have dedicated their attention to the "cough-gastro-oesophageal reflux" relationship, was the first, and with greater continuity, over the years, to have scrupulously maintained this relationship. Already, back in 1990, he firmly sustained that the triade, i.e., comprising gastro-oesophageal reflux, asthma and post-nasal drip, were responsible for the chronic cough presenting in 86% of the patients he had studied, and that gastro-oesophago-laryngeal reflux alone, was the cause of 10-40% of cases presenting with chronic cough [21] [22].

The pathogenetic mechanism by way of which the gastro-oesophago-laryngeal reflux induces cough onset is two-fold and one does not exclude the other:

1a) *lung aspiration syndrome*. In this case, the cough results from aspiration in the broncho-pulmonary tract of large amounts of refluxate. These patients frequently present a considerable reduction in the basal tone of the LES, impaired oesophageal motility and clearance. Endoscopy often reveals 3rd or 4th degree oesophagitis or evidence of Barrett's oesophagus;

1b) *microaspiration syndrome*. This is consistent with the transit across the UES of small amounts of re-

fuxate with inflammation of the laryngeal mucosa with or without bronchial inflammation. Cough and hoarseness are the main symptoms reported by the patient [23];

2) *vagus-mediated oesophago-bronchial reflex mechanism*. This pathogenic mechanism, has only recently been hypothesized, and unlike previous hypotheses, originates from oesophageal receptors for the cough instead of the laryngeal and bronchial receptors. Albeit, this vagal reflex mechanism, once triggered by the reflux, may, theoretically, act via three pathways.

The first consists in stimulation of the receptors (sensori-neural endings) present on the basal layer of the oesophageal epithelium; the nervous stimulation is transferred to the cortical integration centre (nucleus of the single tract) across the branch reaching the vagus nerve. The response, by way of the phrenic nerve, the efferent branch of the vagus, and the recurrent laryngeal nerve, are then sent to the expiratory and laryngeal musculature, respectively.

The second mechanism follows the same reflex arch as the previous one, the only difference being that the efferent branch of the vagus stimulates the mucosal secretion or the release of neurotransmitters into the lower areas with consequent stimulation of the local cough receptors.

The third mechanism involves stimulation of the oesophageal receptor of the cough and transfer of the nervous impulse directly to the trachea, without any integration of the message at central level. At this point, stimulation of the tracheal receptors induces the cough reflex [24-26].

Finally, independently of the pathogenetic mechanism responsible for the cough, a vicious circle is, however, set up which starting from the cough leads to an increase in the trans-diaphram pressure. This phenomenon, in turn, induces relaxation of the LES thus favouring GER which, consequently, contributes to the coughing mechanism.

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