A practical classification of the Empty Nose Syndrome

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The empty nose syndrome (ENS) entails different clinical conditions usually caused by nasal surgery. Many pathogenic factors contribute to the disease progression. Symptoms may be very bothersome and significantly affect the quality of the life. Many therapeutic strategies have been proposed. In this regard, a new multicomponent medical device, containing hyaluronic acid, D-panthenol, vitamin A and E, and biotin, seems to provide promising results.

The term primary atrophic rhinitis defines an umbrella condition including different nasal disorders with unknown origin. On the other hand, secondary atrophic rhinitis is caused by either surgical or non-surgical nasal trauma or may follow a nasal manifestation of a specific systemic disease.

The patient with secondary atrophic rhinitis patients usually presents a number of predisposing factors involved in the symptom complex of atrophic rhinitis. Firstly, surgery for nasal turbinates, mainly concerning the inferior turbinate, represents a leading factor for atrophic rhinitis. In fact, any type of surgical procedure for reducing the turbinate volume, to alleviate nasal breathing obstruction, may induce the "empty nose" syndrome (ENS). ENS produces a secondary atrophic rhinitis which may not occur instantaneously but only materialize years following the initial surgical trauma. Moreover, ENS encompasses multiple pathological forms that are characterized by different anatomy and different clinical pictures. Eugene Kern and Monika Stenkvist initially coined the term ENS in 1994 as a rare but debilitating clinical syndrome that typically occurred after surgical therapy (1). The main symptom is a paradoxical perception of nasal obstruction, despite normal nasal patency (2). Other troublesome complaints include nasal crusting, dryness, nasal discharge, and facial pain (3). Patients with severe ENS may also experience bothered sleep, impaired mental concentration, and choking (4). Psychiatric symptoms may also occur until a suicide attempt (4) as well as neurological dysfunction (5).

From a pathophysiological point of view, ENS follows on from functional interventions on the nasal cavities sometimes performed with too much guilty aggression. Moreover, ENS could also be included in the umbrella definition of secondary atrophic rhinitis. Anyone of the procedures for reducing the turbinate volume, to alleviate nasal breathing obstruction, may induce the ENS, yielding and producing secondary atrophic rhinitis, which may not occur instantaneously

Keywords: empty nose syndrome, turbinates hypertrophy, surgery, classification, phenotyping, medical device

Corresponding Author: Giorgio Ciprandi Via P. Boselli 5, 16146 Genoa, Italy e-mail: gio.cip@libero.it but only materialize years following the initial surgical trauma.

The correct nasal physiology, mainly concerning the function of heating and moistening the inspired air, resides in the lower, middle, and upper turbinates fundamental elements whose conservation must always be considered indispensable. When the nasal physiology, especially in the ventilatory function, is upset by irreversible hypertrophy of the turbinates, it is necessary to proceed with the intervention that must prefer, among the dozens of methods proposed in the literature, that or those useful for unclogging but the most conservative as possible at least respecting the mucosa.

Since anatomical and clinical pictures can be very different, there is the need to define a shared and scientifically based common language for performing comparisons and statistics. Therefore, it seems to be appropriate to propose a classification of ENS that can, at least in general, differentiates post-surgical situations due to the different clinical pictures.

Our proposal derives from hundreds of interventions performed by us in a suitable, safe, and secure environment. This classification is based on endoscopic objectivity and considers five grades (with sub-grades) according to macroscopic features.

Table I shows different characteristics. Figure 1 describes the different grades according to the type of turbinate surgery. Each picture can correspond to a

symptom severity ranging from the annoying comes to be unbearable that can even indicate extreme solutions.

The diversity of symptom characteristics requires differentiation of the term Empty Nose Syndrome so far unable to fully define how important it is to know nor to define the border with the most common Atrophic Rhinitis of different origins. Every grade corresponds to different symptoms. In this regard, a study is ongoing to define the clinical features characterizing the different ENS grades.

Form a clinical point of view; it is clinically relevant to phenotyping patients with ENS to personalize the more appropriate treatment. Lubricants, moisturizing, cytoprotective agents could restore the perception of physiological breathing. In this regard, a new multicomponent medical device seems to be promising, as it contains D-panthenol, hyaluronic acid (HA), vitamin E, vitamin A, and biotin (Rinocross, DMG, Italy).

D-panthenol is the alcohol analog of pantothenic acid (vitamin B_5) and is a provitamin of B_5 . In organisms, it is quickly oxidized to pantothenic acid. It is a viscous, transparent liquid at room temperature. D-panthenol is used as a moisturizer to improve wound healing in pharmaceutical and cosmetic products (6). It improves hydration, reduces inflammation, and accelerates mucosal wounds' rate of healing (7). D-panthenol readily penetrates the mucous membranes (including the intestinal mucosa), quickly oxidized to pantothenic acid. It is also used in



Fig. 1. *Different grades according to the type of surgical turbinate resections. Left panel (grade I); middle panel (grade II); right panel (grades III-V) with arrows indicating the sites of surgical turbinate resection.*

Grade	Characteristics
IA	Single-sided resection of the inferior turbinate
I B	Bilateral resection of the inferior turbinates
II A	Unilateral resection of the inferior and middle turbinates
II B	Bilateral resection of the inferior and middle turbinates
II C	Unilateral resection of the inferior and middle turbinates with ipsilateral meatotomy
II D	Bilateral resection of the inferior and middle turbinates with bilateral meatotomy
III A	Ipsilateral resection of all turbinates
III B	Bilateral resection of all turbinates
III C	Unilateral resection of all turbinates with ipsilateral meatotomy
III D	Bilateral resection of all turbinates with bilateral meatotomy
IV	Resection of all turbinates with the removal of mucosa
V	Resection of all turbinates with septum perforation

Table I. Classification of Empty Nose Syndrome based on grades.

the biosynthesis of coenzyme A, which controls a wide range of enzymatic reactions. HA is a fundamental component of the connective tissue. HA can modulate the inflammatory response, cellular proliferation, and remodeling of the extracellular matrix (8).

Moreover, HA has important lubricant and moisturizing properties. Vitamin E, such as tocopherol, is a fat-soluble antioxidant that can protect the polyunsaturated fatty acids in the membrane from oxidation, regulate the production of reactive oxygen species, and reactive nitrogen species, and modulate signal transduction (9). Moreover, vitamin E has eutrophic property and immune stimulation (10). Vitamin A is a retinoid and is an essential micronutrient for the body and is associated with the proper functioning of the visual system, maintenance of epithelial integrity, red cell production, growth and development, immune and reproductive function (11). In particular, topical application stimulates epithelial growth, fibroblasts, granulation tissue, angiogenesis, collagen synthesis, epithelialization, and fibroplasia (12). These activities concur to repair the mucosal wound. Biotin, such as vitamin H, is a water-soluble B-complex vitamin and is well-known as a co-factor for five essential carboxylases (13). In particular, biotin exerts anti-inflammatory and immune- modulatory activities, relevant in repairing mechanisms of mucosal damage (14). At present, two studies investigated the role of this medical device in

patients with functional impairment after nasal surgery or patients with dystrophic rhinitis (15,16). The outcomes are promising, as this medical device was effective and safe in the large majority of treated patients.

In conclusion, ENS is a complex disorder that challenges the rhinologist. Phenotyping patients could be a reasonable strategy in the workup and management of ENS. Topical medical device with lubricant and hydrating activity could be useful to treat ENS.

REFERENCES

- Scheithauer MO. Surgery of the turbinates and "empty nose" syndrome. GMS Curr Top Otorhinolaryngology Head Neck Surg 2010; 9:Doc03.
- Tam YY, Lee TJ, Wu CC, et al. Clinical analysis of submucosal Medpor implantation for empty nose syndrome. Rhinology 2014; 52:35-40.
- Lee TJ, Fu CH, Wu CL, et al. Evaluation depression and anxiety in empty nose syndrome after surgical treatment. Laryngoscope. 2016; 126(6):1284-9.
- Gill AS, Said M, Tollefson TT, Steele TO. Update on empty nose syndrome: disease mechanisms, diagnostic tools, and treatment strategies. Curr Opin Otolaryngol Head Neck Surg 2019; 27:237-42.
- 5. Li C, Farag AA, Maza G, et al. Investigation of the abnormal nasal aerodynamics and trigeminal functions among empty nose syndrome patients. Int

Forum Allergy Rhinol 2018; 8:444-52.

- Proksch E, de bony R, Trapp S, Boudon S. Topical use of dexpanthenol: a 70th-anniversary article. J Dermatol Treat 2017; 28:766-73.
- Kelly GS. Pantothenic acid. Monograph. Altern Med Rev 2011; 16:263–74.
- Gelardi M, Taliente S, Fiorella ML, Quaranta N, Ciancio G, Russo C, et al. Ancillary therapy of intranasal T-LysYal for patients with allergic, nonallergic, and mixed rhinitis. J Biol Reg Homeost Ag 2016; 30:99-106.
- 9. Khadangi F, Azzi A. Vitamin E The Next 100 Years. IUBMB Life. 2019;71(4):411-415.
- 10. Lee GY, Han SN. The Role of Vitamin E in Immunity. Nutrients. 2018; 10(11):1614.
- Soares MM, Silva MA, Garcia PPC, Silva LSD, Costa GDD, Araújo RMA, et al. Effect of vitamin A

suplementation: a systematic review. Cien Saude Colet. 2017; 24(3):827-838.

- Polcz ME, Barbul A. The Role of Vitamin A in Wound Healing. Nutr Clin Pract. 2019; 34(5):695-700.
- 13. Said HM. Biotin: biochemical, physiological, and clinical aspects. Subcell Biochem. 2012; 56:1-19.
- Mock DM. Biotin: From Nutrition to Therapeutics. J Nutr. 2017; 147(8):1487-1492.
- Maiolino L, La Mantia I, Grillo C, Grillo Ct, Ciprandi G. Functional recovery in subjects undergoing nasal surgery: a new therapeutic strategy. J Biol Reg Homeost Ag (in press).
- Maiolino L, La Mantia I, Grillo C, Grillo Ct, Ciprandi G. Dystrophic rhinitis: etiopathogenetic mechanisms and therapeutic strategy for functional recovery. J Biol Reg Homeost Ag (in press).