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REVIEW ARTICLE

Factors Associated with Gastric and Duodenal Neuroendocrine Tumor Development

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The incidence and prevalence of upper gastrointestinal neuroendocrine tumors (NETs), including gastric NETs (GNETs) and duodenal NETs (DNETs), have been gradually increasing. These trends may be associated with the increased use of health checkups, which includes upper endoscopy, in conjunction with better disease recognition. However, the clinical factors associated with GNETs and DNETs remain unknown; previous studies revealed discrepancies. Recently, metabolic disorders have been indicated as potential factors that are associated with GNETs and DNETs. This review summarizes the results of previous studies and briefly introduces the results of a recent Korean multicenter study on the factors associated with GNETs and DNETs.

Key Words: Neuroendocrine tumors; Stomach; Duodenum; Associated factors

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) originate from enterochromaffin-like cells of the gut or islets of Langerhans of the pancreas. GEP-NETs are heterogeneous in nature based on their primary site [1]. The incidence and prevalence of GEP-NETs has gradually increased over the last three decades. According to recent Surveillance, Epidemiology, and End Result (SEER) data, the annual age-adjusted incidence rate in the United States has increased from 1.09 per 100,000 people (1973) to 6.98 per 100,000 people (2012) [2]. In addition, the prevalence of GEP-NETs has increased from 0.006% (1993) to 0.048% (2012) [3]. The small intestine is the most commonly affected sites, followed by the rectum, pancreas, stomach, and appendix. These recent increases in the number of GEP-NETs may be related to the increased use of endoscopic screening, developments in nuclear medicine, and improved recognition [4,5].

Although the proportion of upper gastrointestinal NET, including gastric and duodenal NETs (GNETs and DNETs, respectively), is relatively low in GEP-NETs, they can be detected in endoscopic screening, and endoscopic resection is a favorable treatment option for small and superficial GNETs and DNETs [6-9]. However, in contrast to many previous studies focusing on the treatment outcome and prognosis of GNETs and DNETs, epidemiologic and clinical factors associated with GNETs and DNETs have rarely been investigated, and there have been some discrepancies between studies [10-14].

Recent studies have shown differences in the natural history and clinical characteristics of GNETs and DNETs [15,16]. However, GNETs and DNETs commonly originate from foregut organs and may share common associated factors, in addition to their site-specific risk factors. In contrast, esophageal NETs are extremely rare compared to GNETs and DNETs, and show relatively aggressive behavior among upper gastrointestinal NETs [17,18]; thus, they will not be covered in this review. Here, we summarize the results of previous studies on factors associated with GNETs and DNETs

and introduce a recent Korean multicenter study on the factors associated with development of GNETs and DNETs.

MAIN SUBJECTS

Previous studies on the factors associated with GEP–NETs

To date, no definite environmental risk factors have been described for GEP-NETs, and previous studies have reported inconsistent and discrepant results [19]. Potential clinical risk factors include a family history of cancer, smoking, alcohol consumption, high body mass index, diabetes mellitus, and medical treatment [20]. In a previous study conducted in the United States, diabetes and a family history of cancer were found to increase the risk of GNETs in women. These findings suggest that the genetic susceptibility of GNETs varies based on sex [10]. Another study from Portugal reported an association between GEP-NETs and obesity with metabolic syndrome components (increased waist circumference, high blood pressure, low high-density lipoprotein [HDL] level, high triglyceride level, and high fasting plasma glucose level) [11]. Another study from Israel reported the risk factors for GEP-NETs by case-control analysis, and GNETs were associated with obesity (high body mass index) and height, whereas small bowel NETs were associated with male sex [12]. A recent study suggested that metabolic syndrome is associated with aggressive behavior in GEP-NETs [21]. These studies show that metabolic disorder-associated systemic inflammation could affect the development of GEP-NETs. However, most studies included various types of GEP-NETs, and were performed at a single center in Western countries. In addition, only a small number of GNETs and DNETs were included in these studies, making it difficult to apply these findings to patients with GNETs and DNETs, especially in Korea.

Disease characteristics of GNETs

GNETs are classified according to the WHO classification based on Ki-67 expression and mitotic index [19]. In addition, the treatment and prognosis of GNETs varies according to the different subtypes, based on serum gastrin and gastric pH levels [6]. Classification of GNET has not been well established, but usually type 1 GNETs account for 70–80% of cases and are associated with chronic atrophic gastritis (CAG). The absence of gastric acid is associated with autoimmune CAG, which destroys gastric parietal cells and stimulates antral G cells, thereby causing hypergastrinemia. Type 1 GNETs usually present as small, multiple tumors; therefore, endoscopic resection is a feasible treatment option for small, superficial GNETs. The overall prognosis is favorable, with an excellent 5-year survival rate (90–95%) [3]. Type 2 GNETs are the rarest subtype and are associated with hyperchlorhydria, hypergastrinemia, gastrinoma, and multiple endocrine neoplasia. They are commonly associated with peptic ulcer disease and Zollinger-Ellison syndrome, and their overall prognosis shows favorable 5-year survival rate (70–90%) [3]. Type 3 GNETs occur sporadically and are not usually accompanied by hypergastrinemia or CAG. They show high malignant potential and early lymph node metastasis. Thus, in contrast to type 1 GNETs, surgical resection is primarily considered, even at an early stage. Type 4 GNETs refer to poorly differentiated neuroendocrine carcinoma (NEC) showing very aggressive behavior, and frequent lymph node and liver metastases which are associated with a poor prognosis. Recent 2019 WHO classification specified poor differentiated NEC as small-cell type NEC and large-cell NEC, respectively, and introduced mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) as a new category (Table 1) [6,22,23].

Disease characteristics of DNETs

DNETs frequently arises in the bulb (58%) and second portion (33%), whereas NETs in the ampulla of Vater (20%) are considered separate disease entities. From a histopathological perspective, in addition to the WHO classification, four subtypes have been suggested: gangliocytic paragangliomas, gastrinomas, ampullary-type somatostatin-producing tumors, and ordinary non-functioning NETs [9]. Unlike that surgical resection is generally recommended for ampul-

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Table 1. Characteristics of Subtypes and Classification of Grading for Gastric Neuroendocrine Tumors

	Gastric NETs			Gastric NECs	Others
	Type 1	Type 2	Type 3	Type 4 (Small-cell type NEC, Large-cell type NEC)	MiNEN
Relative frequency	70–80%	5–6%	14–25%	6–8%	
Features	Mostly small (< 1–2 cm) and multiple	Mostly small (< 1–2 cm) and multiple	Solitary, often > 2 cm	Solitary mostly exulcerated, 2 cm	
Associated condition	CAG	MEN1/ZES	No	No	
Histology	Well differentiated, G1–3	Well differentiated, G1–3	Well differentiated, G1–3	Poorly differentiated, G3	Well or poorly differentiated, G1–3
Serum gastrin	(Very) high	(Very) high	Normal	(Mostly) normal	
Gastric pH	Anacidic	Hyperacidic	Normal	(Mostly) normal	
Metastases	< 10%	10–30%	50–100%	80–100%	
Tumor-related deaths	No	< 10%	25–30%	≥ 50%	

CAG, chronic atrophic gastritis; G1, low grade (mitotic rate < 2, Ki-67 index < 3%); G2, intermediate grade (mitotic rate 2–20, Ki-67 index 3–20%); G3, high grade (mitotic rate > 20, Ki-67 index > 20%); MEN1, multiple endocrine neoplasia type 1; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; ZES, Zollinger-Ellison syndrome.

lary NETs regardless of tumor size, endoscopic resection is recommended for small, superficial DNETs that have a low tendency to metastasize and show favorable outcomes [8].

Recent Korean studies on the factors associated with development of GNETs and DNETs

Considering the paucity of related studies, this multicenter case-control study was conducted to evaluate the factors associated with development of GNETs and DNETs [24]. A total of 396 patients with GNETs and 193 patients with DNETs were included in the case group. Clinical and laboratory characteristics were compared and evaluated in a control group of 1,725 healthy controls. Multivariate analyses showed that age, diabetes, hypertension, low serum HDL levels, and past/present *H. pylori* infection were associated with GNETs, whereas diabetes, hypertension, low serum HDL levels, and past/present *H. pylori* infection were associated with DNETs. In addition, sex-specific differences were observed in both GNETs and DNETs. This study showed that several metabolic factors could affect the development of GNETs and DNETs and suggested the necessity of personalized and sex-specific approaches for patients with GNETs and DNETs.

CONCLUSION

While there are limited data on the factors associated with GNETs and DNETs, conflicting results have been reported. Notably, common metabolic disorders such as diabetes, hypertension, and low serum HDL levels were significantly associated with both GNETs and DNETs. Furthermore, sex-specific associations in both GNETs and DNETs were suggested, highlighting the need for personalized and sex-specific approaches for the management of GNETs and DNETs. Further studies are required to understand better and validate these findings.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Kwangwoo Nam, Su Youn Nam. Data acquisition: Kwangwoo Nam. Formal analysis: Kwangwoo Nam, Su Youn Nam. Funding: Su Youn Nam. Supervision: Su Youn Nam. Writing—original draft: Kwangwoo Nam. Writing—review & editing: Kwangwoo Nam, Su Youn Nam.

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