Epidemiology of Neuroendocrine Tumors in an Iranian Population

Mona MalekZadeh1, Sam Alahyari2, Saleh Sandoughdaran1,3, Hanieh Zham4

Abstract
Neuroendocrine tumors (NETs) are rare and heterogeneous group of malignancies most commonly found in the gastrointestinal system. In this study, we examined the epidemiology of NETs in an Iranian population. The incident NET cases diagnosed between January 1, 2009 and December 31, 2014 were collected from databases of three hospitals in Tehran (Shoada-e-Tajrish Hospital, Imam Hossein Hospital and Pars Hospital). A total of 291 cases with NET diagnosis were identified. The most common NET location was gastrointestinal (71.4%), followed by Bronchopulmonary (7.2%) and Genitourinary (7.2%). The total number of identified NETs in our study increased from 25 cases in 2009 to 66 cases in 2014. In conclusion, our data suggests that the incidence of NETs is increasing slowly. Thus, etiologic studies for NETs are needed to help plan future preventive strategies.

The authors declare no conflicts of interests

Keywords: Epidemiology, Iranian population, neuroendocrine tumors


Introduction
Neuroendocrine tumors (NETs) are rare malignancies of the neuroendocrine system, which are defined as epithelial neoplasms with predominant neuroendocrine differentiation.1,2 Due to their heterogeneity, neuroendocrine neoplasms do not have a single unified system of nomenclature, grading or staging and despite their identification more than a century ago, the first World Healthcare Organization (WHO) classification of NETs was not established until 1980.3 Many neuroendocrine neoplasms have been traditionally called “carcinoids,” but this term does not accurately reflect their variable biology, histologic differentiation, and secretory potential.4 NETs are generally known as slowly growing tumors, with approximately 4–5 years from the onset of symptoms to diagnosis.5 These tumors may secrete specific peptide hormones or bio-amines such as insulin, glucagon, somatostatin, VIP (vasoactive intestinal peptide), serotonin, and gastrin some of which may cause clinical symptoms (also known as “functioning” NET). Because these cancers arise across the diffuse neuroendocrine system, NETs may develop at any site, but the most common sites are the gastrointestinal tract and the bronchopulmonary tree.6–10 They can also originate in other areas, including the pancreas, larynx, ovaries, thyroid, pituitary, and adrenal glands.11 Neuroendocrine tumors account for only 0.5% of all malignancies and their incidence rate is below 1.4 cases per 100,000 persons.12 The lowest incidence has been reported in Italy,13,14 and the highest in the USA, especially among African-Americans.12 According to several reports, the incidence of NETs has been rising in the last decades.7–9,15,16 This might be due to greater awareness of the disease, improved diagnostic tools or a change in definition of NETs. Despite the racial difference in the incidence of NETs, there is a paucity of data to describe the epidemiology of NETs in Iran. In the present study, population-based data from three large hospitals are used to describe epidemiologic features of NETs in an Iranian population from 2009 to 2015.

Material and Methods
The frequency of NET cases diagnosed between January 1, 2009 and December 31, 2014 and total number of samples were collected from databases of Shoada-e-Tajrish Hospital, Imam Hossein Hospital and Pars Hospital by a physician. All collected data were reviewed by an oncologist. Shoada-e-Tajrish Hospital and Imam Hossein Hospital are both referral public hospitals and Pars is a private hospital. Carcinoid tumors of uncertain malignant potential, enterochromaffin cell carcinoid, enterochromaffin-like cell tumors, goblet cell carcinoid, tubular carcinoid, neuroendocrine carcinoma, atypical carcinoid, islet cell tumors, insulinoma, glucagonoma, gastrinoma, VIPoma, somatostatinoma, enteroglucagonoma, and mixed islet cell and exocrine adenocarcinoma were included. For immunohistochemical analysis, Chromogranin, Synaptophysin, CD56 or CD57 were used to confirm diagnosis.17 Information on tumor site was obtained from pathologic reports. Pathologic data of Imam Hossein hospital specimens was not available for 2010 through 2011.
Results

Between January 1, 2011 and December 31, 2014, a total of 291 cases with NET diagnosis were identified. The frequencies of NETs, and percentages of total NETs registered are shown in Figure 1. The most common NET location was gastrointestinal (208 cases, 71.4%), followed by Bronchopulmonary (21 cases, 7.2%) and Genitourinary (21 cases, 7.2%). It is of note that in 11.6% (24 cases) of patients presenting with metastases the primary site remained unknown.

The trends presented in Figure 1 indicate an increase of total NETs in our study increased from 25 cases in 2009 to 66 cases in 2015 (Figure 1A and Table 1). This increase was further confirmed by dividing the total number of NETs by total number of pathology samples for each year. The incidence of all of the more common NETs appears to be increasing and is most evident for gastrointestinal NETs (Figure 1B). As data from Imam Hossein Hospital were missing for 2010 through 2011, we omitted those years from Figure 1.

Discussion

To the best of our knowledge, this is the first study describing the epidemiologic features of neuroendocrine tumors in an Iranian population. Using three data from large hospitals, we observed that the frequency of NETs in Tehran increased steadily from 2009 to 2014. This increase was further confirmed by comparing the proportion of NETs and total number of samples for each year. A comprehensive survey performed by Modlin et al. on 13,715 carcinoid tumors from 1973 to 1999 using data from the US Surveillance, Epidemiology, and End Results (SEER) program of

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<td>26</td>
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GI = gastrointestinal; GU = genitourinary; BP = bronchopulmonary; UK = unknown origin; IH = Imam Hossein Hospital; P = Pars Hospital; SH = Shohada-e-Tajrish Hospital

Figure 1. Incidence of neuroendocrine tumors (NETs) in three hospitals in Tehran, 2009-2015. (A) Total number of NETs by year. (B) Total number of NETs divided by Total number of samples for each year. (C) Frequency of neuroendocrine tumors (NETs) over time, by site
Similar results have been observed by others. Possible reasons for this rise include increasing use of immunohistochemistry in diagnostic pathology, improvements in diagnostic imaging, particularly computed tomography and gastrointestinal endoscopy leading to the incidental finding of asymptomatic NETs, and an actual increase in NET incidence.

While there seems to be an overall rise in the incidence rates of NETs, this increase differed by body sites. In our analysis, we found that the fastest rise in the frequency of NETs pertained to bronchopulmonary and gastrointestinal tumors which is similar to results reported in US and Australian populations. It is not clear why the rise in the incidence rate of NETs occurs faster for certain body sites, but some reports have proposed increase in common risk factors, such as tobacco smoking as the primary cause. Other reasons such as increasing use of diagnostic imaging techniques like abdominal sonography might also explain this observation.

The distribution of NETs by site in this study was similar to those reported for other populations. Gastrointestinal and bronchopulmonary are reported as the main sites of NET in Norway (50% and 21%), US Whites (50% and 21%), Taiwan (49.4% and 20%), and Turkey (47.6% and 25.9%). The distribution of NETs can be explained by the fact that these tumors derive from enterochromaffin cells and their frequency of occurrence correlates with the site-density of neuroendocrine cells. Hence, most of the NETs arise from the gastrointestinal tract, which is the largest endocrine organ in the body, or the bronchopulmonary system, which contains a high density of Kulchitsky cells in the respiratory epithelium.

The main limitation of this study is that it relies on pathology report of three hospitals which may not reflect the true epidemiologic features of NETs in the Iranian population. Furthermore, a limitation of data from retrospective studies is that probably not all tumors are collected and some types of tumors are not properly described in pathology reports, which could have led to an underestimation of the actual incidence – an issue for all previous studies, as well.

In conclusion, our data suggests that the incidence of NETs is increasing slowly. Thus, further observations in larger studies are needed to evaluate the real incidence trend and to detect changes in prognosis of NETs to help plan future preventive strategies.

References