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Original Article

Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: A nationwide study and systematic review

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ABSTRACT

Introduction: Recent years have seen major changes in clinical practice which may have affected the incidence rates of pheochromocytoma(PCC)/sympathetic paraganglioma(sPGL). There is, however, a lack of up-to-date information describing trends in these incidence rates.

Methods: We searched the Dutch pathology registry to identify all histopathologically confirmed cases of PCC/sPGL diagnosed between 1995 and 2015. We calculated incidence rates according to age category as well as age-standardized incidence rates (ASR). We also searched Medline and Embase to find data on nationwide incidence rates of PCC/sPGL.

Results: The nationwide pathology study revealed a total of 1493 patients with either PCC or sPGL. The ASR for PCC increased from 0.29 (95% CI: 0.24–0.33) to 0.46 (95% CI: 0.39–0.53) per 100,000 person-years in the periods 1995–1999 and 2011–2015, respectively. For sPGL the ASR in these same periods were 0.08 (95% CI: 0.06–0.10) and 0.11 (95% CI: 0.09–0.13) per 100,000 person-years, respectively. Concomitantly, PCC size decreased (β −0.17; P < .001) and age at diagnosis increased (β 0.13; P = .001). Our systematic search yielded 3 papers reporting on a total of 530 PCC/sPGL cases, showing a combined annual incidence rate varying from 0.04 to 0.21 per 100,000 person-years.

Conclusion: Incidence rates of PCC/sPGL have increased significantly over the past two decades. This trend coincides with a higher age and a smaller tumor size at diagnosis. Most likely these observations are at least in part the result of changes in clinical practice during the study period, with a more intensified use of both imaging studies and biochemical tests for detecting PCC/sPGL.

1. Introduction

Pheochromocytomas (PCC) and sympathetic paragangliomas (sPGL) are rare neuroendocrine tumors derived from chromaffin tissue of the adrenal medulla and the extra-adrenal sympathetic paraganglia, respectively. Histologically these tumors are identical and they share the capacity to synthesize and release catecholamines (dopamine, norepinephrine and epinephrine) [1–3]. Uncontrolled hypersecretion of catecholamines by these tumors may evoke typical signs and symptoms such as paroxysmal hypertension, sweating and tachycardia, and can result in severe cardiovascular morbidity and mortality [4]. Surgical resection is the treatment of choice, as it represents the only option for cure [5].

In the past, a substantial proportion of PCC/sPGL was not diagnosed during life but discovered post mortem during autopsy [6]. Recent years have seen a tremendous rise in the number of imaging studies being ordered in clinical practice [7, 8], as well as more frequent assessment of metanephrines in plasma or urine [9]. The sensitivity of biochemical testing and imaging techniques for detecting PCC/sPGL has also improved substantially over the past two decades [10–12]. It is conceivable that these changes in diagnostic procedures have influenced the detection rate of PCC/sPGL during life in recent years. However, epidemiological data on PCC/sPGL, and particularly on its incidence rate, are surprisingly scarce.

Our objective was to determine the annual incidence rate of PCC/sPGL during the past two decades in the Netherlands. To this end we conducted a retrospective nationwide pathology study. We hypothesized that the annual incidence rate has increased during the past two

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decades. For comparison of our data, we performed a systematic review of the literature on previously reported nationwide incidence rates of PCC/sPGL.

2. Methods

2.1. Systematic review

In order to identify articles published in peer-reviewed medical journals we conducted a systematic search of PubMed/MEDLINE and Embase, in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13]. We used the following search terms: pheochromocytoma, paraganglioma, epidemiology, incidence, prevalence, autopsy, and post mortem examination (see Supplemental data for detailed information). The search was carried out on November 10, 2016. We considered articles to be eligible for inclusion if they reported original research data on nationwide annual incidence rates of PCC and sPGL, or both, and were published in the English, German, French, Spanish or Dutch language. To avoid the risk of referral and migration bias we excluded papers reporting incidence rates derived from cases collected in one or more centers or only in a certain geographical region. We likewise excluded papers that exclusively described autopsy series without reporting estimates of nationwide incidence rates.

Two authors (A.B. and E.B.) independently and in duplicate assessed the eligibility of all papers. Titles and abstracts were screened first. Next, full-text articles were retrieved of potential relevant articles and these were thoroughly assessed. Articles were also searched for relevant references. If titles and abstract screening were inconclusive the full-text article was evaluated for eligibility. One reviewer extracted data including study design, national annual incidence rates of PCC/sPGL, and demographics of the study participants. The second reviewer checked the accuracy of the extracted data. The primary endpoint of this systematic review was the nationwide annual incidence rate of PCC/sPGL.

For each study we considered the following risks of bias: completeness and reliability of data acquisition and reporting of the primary endpoint, duration of the study period, and selection of the population. We graded the quality of the reported data according to the Oxford Centre for Evidence-Based Medicine levels of evidence [14].

2.2. Nationwide pathology study

We searched the Dutch Pathology Registry (PALGA) to identify all histologically proven PCC and sPGL diagnosed in the Netherlands between January 1, 1995 and December 31, 2015. The PALGA registry is a nationwide network and registry of histo- and cytopathology in the Netherlands, with coverage dating back to 1991 [15]. We conducted a systematic analysis of the PALGA registry, using the following search terms: adrenal, adrenal medulla, pheochromocytoma(s) and paraganglioma(s). This search yielded a list of excerpts, i.e. summaries of the original pathology reports, including a limited amount of anonymized patient data. We labeled each excerpt with a unique patient identification number. It is worth noting that if the pathology material was obtained from different anatomical locations or at separate dates a single patient could have more than one excerpt in the PALGA registry.

Two reviewers (A.B. and E.B.) independently evaluated all excerpts and included those describing a diagnosis of PCC/sPGL. Excerpts reporting on pathology material offered for revision were excluded. We also excluded excerpts describing residual or recurrent disease, defined as a tumor resected from the same anatomical location as the first PCC/sPGL within or after 6 months of the initial resection, respectively. We also excluded metastatic lesions. A lesion was considered metastatic when PCC/sPGL tissue was reported to be present in nonchromaffin tissues such as lymph nodes, liver, lung or bones [3, 16]. Furthermore, we excluded excerpts describing only cytology specimens and material offered for either additional immunohistochemistry staining or research purposes. Excerpts reporting a sPGL located in the aortopulmonary window were excluded as differentiation between sPGL and parasympathetic PGL was not feasible in the absence of clinical information [3]. If the information provided in the excerpt was not sufficient, the original histopathology report was requested for further study. If the original histopathology report did not permit a definite diagnosis, an experienced pathologist (R.K.) re-examined the original pathology specimens.

Demographic data and tumor specifications were extracted from the excerpts sPGL were further subdivided by localization according to the World Health Organization (WHO) classification of endocrine tumors [3]. A spinal localization was defined as a well-demarcated intradural or extradural mass without infiltration of spinal cord, soft tissues or bone [17]. Bilateral PCC was subdivided into synchronous and metachronous presentation, defined as resection of the second PCC less or > 6 months after the preceding contralateral adrenalectomy, respectively. In accordance with the Dutch Medical Research Involving Human Subjects Act, this study has been exempted from approval by the medical ethics committee.

For each study year we calculated age-specific incidence rates for PCC, sPGL, and PCC/sPGL combined. We subsequently determined an age-standardized incidence rate (ASR) for each year by calculating a weighted mean of the age-specific incidence rates, according to the standardized European population, in order to correct for changes in age distribution over time [18]. In order to comprehensively delineate age-specific changes, we defined larger age categories as follows: 0–24, 25–49, 50–74, and 75 years or older. Age group specific incidence rates and their ratios were determined. We also calculated ASR and age-group specific incidence rates over the first and last 5 years of the study period. We obtained the required demographic data for these calculations from Statistics Netherlands.

In order to investigate a possible shift from post mortem towards ante mortem diagnosis, we calculated the incidence rate of post mortem diagnosed PCC/sPGL per annum. Annual autopsy rates were calculated as the percentage of deceased individuals per annum in the Dutch population in whom an autopsy had been performed. We derived the number of clinical autopsies performed for each year from PALGA, in collaboration with the Dutch Society for Pathology.

Data are expressed as mean with 95% confidence interval (CI) or median with interquartile ranges [IQR], where appropriate. Distributions were analyzed using the Chi-square test. Univariate relationships were determined using Pearson's or Spearman's correlation coefficients, where appropriate. Multivariate linear regression analyses were carried out to disclose the relationship between year of diagnosis, post mortem incidence rate, and autopsy rate. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corporation, Chicago, IL, USA). A two-sided P-value < .05 was considered significant.

3. Results

3.1. Systematic review

After removal of duplicates, the literature search yielded 2095 papers. After reading titles and abstracts we excluded 2025 articles. We excluded an additional 67 papers after reading the full texts (Supplemental Fig. 1). We finally included three papers in the present systematic review [19–21].

The three publications included in this systematic review were published between 1964 and 1988. Two of the three used a national disease registry for data extraction. One study used a questionnaire to identify cases retrospectively and probably suffered from recall bias. Nevertheless, we considered the risk of publication bias and selective reporting to be low.

Collectively, these three studies comprised a total of 530 PCC/sPGL