For the Forthcoming Winning Shot in the Battle against Cushing Disease

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Cushing disease (CD), primarily caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, presents significant challenges clinicians due to its complex presentation and management. The intricate balance necessary for managing the accompanying hypercortisolemia along with its extensive effects on metabolism, cardiovascular health, immune function, neurocognitive functions, and the consequent increased mortality risk, demands a multifaceted and nuanced approach. “An individualized approach to the management of Cushing disease,” by Fleseriu et al. [1] provides an extensive review that expertly outlines the current state of knowledge and proposes a tailored approach for treatment, with strong emphasis on the need for a patient-centered strategy.

Since the first case of Cushing syndrome (CS) first reported by Dr. Harvey Cushing in 1912 [2], ACTH-producing pituitary adenomas have traditionally been recognized as the most common cause of endogenous CS, accounting for approximately 60% of cases [3]. However, due to its rarity, comprehensive epidemiological data on CD are scarce. Most publications reporting epidemiologic data on CD focused on the entire spectrum of endogenous CS, while only a few studies have selectively investigated the epidemiology of CD (Table 1) [4-8]. A population-based study in Spain, conducted between 1975 and 1992, reported an annual incidence of 2.4 cases per million and a prevalence of 39.1 cases per million for CD [4]. The National Patient Register of the Danish National Board of Health, covering the years 1985 to 1995, found that the annual incidence was 1.2 (1985 to 1990) and 1.7 cases (1991 to 1995) per million [5]. In Korea, the Survey Committee for Endocrine Diseases in the Korean Endocrine Society conducted a nationwide survey to collect clinical data from patients diagnosed with endogenous CS between 1992 and 1998. In total, 180 cases of endogenous CS from 51 university hospitals in Korea were collected and analyzed, yielding an annual incidence of 0.84 cases per million. The proportion of CD was 48.3%, similar to that of adrenal CS (48.9%) [9]. The nationwide, population-based study assessed the incidence and prevalence of Cushing’s disease using claims data from the Korean Health Insurance Review and Assessment Service database between 2013 and 2017, after deidentification.

Table 1. Incidence and Prevalence of Cushing Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Annual incidence, /million persons</th>
<th>Prevalence, /million persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindholm et al. [5]</td>
<td>Netherland</td>
<td>1.2 (1985–1990)</td>
<td>-</td>
</tr>
<tr>
<td>Ragnarsson et al. [8]</td>
<td>Sweden</td>
<td>1.6 (1987–2003)</td>
<td>-</td>
</tr>
<tr>
<td>Broder et al. [7]</td>
<td>United States</td>
<td>6.2 (2009)</td>
<td>-</td>
</tr>
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</table>

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This study reported an annual incidence of CD of 2.3 cases per million with the prevalence of 9.8 cases per million in Korea [6]. As noted in a review article [1], a higher incidence rate of 6.2 and 7.6 cases per million persons in 2009 and 2010, respectively, was reported in the United States based on the health insurance database [7]. However, it is uncertain whether this increase has increased with time or the consequence of methodological difference [10].

The process of diagnosing CD has been detailed extensively through numerous studies and previous clinical guidelines. However, past guidelines have not thoroughly addressed the methods for assessing treatment efficacy and evaluating recurrence after initial treatments such as surgery. In this regard, this review article is particularly valuable for clinicians diagnosing and treating CD, as it provides detailed information based on previous research results. Notably, the article extensively addresses the criteria for determining remission and recurrence, and highlights differences in assessing the efficacy of post-surgical versus medical treatments [1]. Unfortunately, measuring late-night salivary cortisol, the first indication of recurrence, is not widely available in Korea. The article also provides detailed information on various medical treatment options that can be considered for those without remission or with recurrence detected after the initial surgical treatment for CD. Additionally, it emphasizes the importance of an individualized approach tailored to the characteristics of each patient [1]. Although several medications, such as levoketoconazole, osilodrostat, and mifepristone, are already being used to treat CD in other countries, once again, none of them are available in Korea, leading to inevitable frustration. Finally, with the overall increase in life expectancy, the number of elderly patients with CD is expected to rise. Therefore, understanding treatments according to the characteristics of these patients will be crucial. By sharing the authors’ clinical experiences, this review is expected to greatly assist many clinicians in managing such elderly patients.

As emphasized in the article by Fleseriu et al. [1], despite recent advancements in diagnostic technologies and therapeutic agents, CD remains one of the most challenging diseases to manage. Therefore, multidisciplinary care is essential, and an individualized therapeutic approach tailored to the patient’s specific characteristics is imperative. The original article strongly supports this viewpoint, a perspective with which I also fully agree with. In summary, the review article by Fleseriu et al. [1] provides an invaluable resource for clinicians managing CD. It highlights a shift towards a more personalized treatment framework that accommodates the wide variability in clinical presentations and patient responses to treatment. The insights provided by this review should catalyze further research and innovation in the management of CD, with the ultimate goal of enhancing patient outcomes and quality of life.

CONFLICTS OF INTEREST

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

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