Epidemiology of Castleman Disease

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KEYWORDS

• Unicentric Castleman • Multicentric Castleman • TAFRO • HHV-8

KEY POINTS

- The incidence of unicentric Castleman disease is 15 per million patient years.
- The incidence of idiopathic multicentric Castleman disease is 5 per million patient years, but with regional variation.
- Human herpesvirus-8 (HHV-8) plus multicentric Castleman disease is most common in men infected with HHV-8 HIV and is more common in the era of highly active antiretroviral therapy.

Accurate assessment of the epidemiology of Castleman disease (CD) has been hampered by lack of an International Statistical Classification of Diseases and Related Health Problems (ICD) code and no formal definition of the disease. However, the ICD code (ICD-10-CM D47.Z2), which became effective on October 1, 2016, and published the diagnostic criteria,[1] will allow improved data regarding this of the cluster of diseases that make up this rare entity. Estimates of the incidence of CD vary widely. In an attempt to better determine the incidence, a systematic search of a claims database was undertaken.[2] Two commercial insurance claims databases, IMS LifeLink and Truven Health Analytics MarketScan, which together include medical records on nearly 200 million people, were screened for patients with an index diagnosis of lymphadenopathy (ICD-9 code 785.6) who were enrolled for 1 year before or 2 years after the index diagnosis. This was done to ensure that there was an opportunity to meet the CD characteristics as published in 2005.[3] Patients were excluded if they did not have a lymph node biopsy because this is required for CD diagnosis. Those with rheumatoid arthritis, lupus, cancer (including lymphoma), and human immunodeficiency virus (HIV) were also excluded. The estimated incidence rate for CD was 21 (IMS LifeLink) to 25 (MarketScan) per million person-years. Applying this rate to the US population 25 years and older (assumed to be 207,301,600 in 2011), the incidence of CD in the United States is 4353 to 5183 patients. To try to estimate the proportion of these patients who had multicentric CD (MCD), MCD was assumed to be the

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diagnosis if patients had been treated with doxorubicin, dexamethasone, prednisone, or rituximab, which are drugs that were commonly given for MCD between 2001 and 2009, the years analyzed in the review.[4] It was estimated that 23% of patients with CD were potentially suffering from MCD, equating to 1001 to 1192 cases in the United States, with the other 77% assumed to have unicentric CD (UCD). There are several assumptions in this algorithm, hence the confidence limits of this estimate remain very wide. However, the numbers estimated are remarkably similar to those obtained using other methodologies.

An alternative approach to estimate the incidence of MCD in the Asia-Pacific region involved a survey of centers in Southeast Victoria (Monash Health System), Australia (subsample number [n] = 10); Hong Kong, China (n = 1); and Auckland, New Zealand (n = 1). This produced an average MCD point prevalence estimate of about 5 per million.[5] All regions surveyed had similar estimates ranging from 4.2 to 5.4 per million. The proportion of cases that are multicentric can vary by ethnicity and higher rates are reported in Polynesians living in New Zealand[6] (see later discussion).

The 3 main broad subtypes of CD each have distinctive etiologic factors and so it is important to consider them separately. These include (1) UCD, (2) human herpesvirus-8 (HHV-8) plus MCD (HHV-8+MCD), and (3) idiopathic MCD (iMCD). In addition to these broad groups, there seem to be other distinct subtypes of iMCD. These include (1) polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell neoplasm, and skin changes (POEMS) related MCD; and (2) thrombocytopenia, anasarca, fever, renal insufficiency, and organomegaly (TAFRO) syndrome. The term oligocentric or regional CD has also been proposed for a subtype of UCD with clusters of regionally confined nodes.[7]

UNICENTRIC CASTLEMAN DISEASE

UCD can present at any age, from the very young to the elderly, but it predominantly presents at a younger age than MCD. A literature review was performed to identify reported cases of CD and was published in 2012.[8] Of 404 cases, 274 or 68% had UCD. The median age at presentation was 34 years with a wide age range (2–84 years) and a mild female predominance (60%). This is almost identical to a North American series of 54 patients from the Mayo clinic and the University of Nebraska (**Fig. 1**). The median age in this series was 34 years (range 4–74 years), including 4 cases in patients younger than 10 years of age.[9] Additional cases have been reported in children as young as 2 years of age.[10] A series from Beijing, China, of 145 HIV-negative patients, clinically classified 69 (47.6%) cases as UCD[11] (**Fig. 2**). The median age was 40 years for the whole group, with an even sex distribution (52% female).

UCD is thought to be rare, with no reliable estimates of its incidence in the population (to date). The insurance claims database screening study estimated the rate at 16 per million.[2] Smaller case series have the potential for referral bias because MCD cases are more difficult to manage and more likely to be referred to a center of excellence, skewing the relative proportion of the 2 entities. There seems to be similar incidence and pattern of disease in series reported from the United States,[9] China,[11] Czechoslovakia,[12] Japan,[13] and New Zealand.[6]

A small number of cases, perhaps 5% to 10% of UCD, present with regionally clustered nodes. These patients more often have systemic symptoms of anemia, high C-reactive protein (CRP), and low albumin, in keeping with high levels of interleukin (IL)-6. Immunoglobulins are not increased. Seen in both younger and older patients, there are insufficient data to determine if this is a different entity and the incidence, sex, and age distribution.