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Pediatric histiocytoses in the United States: incidence and outcomes

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ABSTRACT

Background: Histiocytoses are rare disorders affecting the pediatric population.
Materials and methods: Surveillance, Epidemiology, and End Results database was searched for pediatric cases (<20 y old) of histiocytosis diagnosed between 1973 and 2010. Demographics, clinical characteristics, and survival outcomes were analyzed using standard statistical methods. Class I disease (Langerhans cell histiocytosis) and class III (malignant histiocytosis) were included in the data set.
Results: A total of 828 cases were identified. Overall incidence was 0.142/100,000 persons per annum. Incidence was highest in younger children and those of Asian or Native American descent. Class III disease had a higher incidence *versus* class I. Adolescents tended to present with class III, whereas young children presented with class I. Disseminated disease was present in most cases of class III, whereas class I had more localized cases. Surgical excision was more likely to be performed in class I. Overall median survival was 349 mo. Patients 15–19 y old and children <1 y old had the worst outcomes. Class I had higher survival compared with class III, which had a median survival of 33 mo. Cases with hematologic spread carried the worst prognosis. Surgical excision conferred a survival advantage while radiation had no effect. Survival improved over the study period. Gender and race had no association with survival.
Conclusions: Class I disease had localized cases and showed benefit from surgical intervention. Class III disease had a higher incidence and was associated with disseminated disease and lower survival. Radiation therapy did not affect survival. Overall survival increased over the previous 40 y.

1. Introduction

Histiocytosis is a rare disease characterized by an abnormal proliferation of histiocytes. These cells can be grouped into two main categories: tissue macrophages and dendritic cells, depending on their morphological, functional, and immunohistochemical properties. The associated disease is divided into three major classes: I, II, and III. Previously, they

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Table 1 – Histiocytic disorders classification table.

Disorders of varied biological behavior		Malignant disorders
Class I	Class II	Class III
Dendritic cell-related	Macrophage-related	Monocyte-related
Langerhans cell histiocytosis	Hemophagocytic syndromes	Leukemias (French–American–British [FAB] and revised FAB classifications)
Secondary dendritic cell processes	Primary hemophagocytic lymphohistiocytosis (familial and sporadic; commonly elicited by viral infections)	Monocytic leukemia M5A and B
Juvenile xanthogranuloma and related disorders	Secondary hemophagocytic syndromes (infection associated, malignancy associated, and other)	Acute myelomonocytic leukemias M4
Solitary histiocytomas of various dendritic cell phenotypes	Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy)	Chronic myelomonocytic leukemias
	Solitary histiocytoma with macrophage phenotype	Extramedullary monocytic tumor or sarcoma (monocytic counterparty of granulocytic sarcoma)
		Dendritic cell-related histiocytic sarcoma (localized or disseminated)
		Specify phenotype, follicular dendritic cell, interdigitating dendritic cell, etc.
		Macrophage-related histiocytic sarcoma (localized or disseminated)

Adapted from the study by Favara, *et al.* [7].

corresponded to Langerhans cell histiocytosis (LCH), histiocytoses of mononuclear phagocytes, and malignant histiocytosis (MH), respectively [1]. Over the past several decades, however, these classes have been broadened by the inclusion of additional distinct cell-type disorders. A contemporary classification scheme of the histiocytoses can be seen in Table 1. These disorders are uncommon and predominately found in childhood. Because of their rarity, their incidences and outcomes are sparsely documented [2].

LCH is the most common subtype of the class I disorders. It tends to affects young children and may present as a multisystemic syndrome. The more benign and localized forms of LCH present with unifocal or multifocal osseous lesions, most frequently involving the skull [3–6]. MH, or class III, is an umbrella term used to describe the malignant transformation of histiocytes. This type often has a disseminated nature, affecting multiple organ systems, including the liver, spleen, lymph nodes, skin, bone, and lungs [1,7–10]. This syndrome should not be confused with the multisystemic form of LCH, which is a separate entity.

Bony lesions, specifically those affecting the calvarium, are not uncommon in histiocytosis. Calvarial lesions arise in up to 70% of patients diagnosed with bony LCH [11]. Although some lesions may be left for observation, many require major excision. This procedure can pose great challenges requiring a multidisciplinary approach. Therefore, an improved understanding of this disease is crucial for effective treatment. For this purpose, we analyzed data from the largest available national cancer registry to delineate the epidemiology and clinical outcomes of pediatric histiocytoses in the United States.

2. Materials and methods

The Surveillance, Epidemiology, and End Results (SEER) database April 2013 release was used to identify and analyze cases of pediatric histiocytosis in the United States diagnosed between 1973 and 2010. The database contains information on class I or III histiocytic disorders only. Because SEER uses the International Classification of Diseases for Oncology, 3rd revision to classify diseases and does not make a distinction between histiocytic disorder subtypes, we considered LCH synonymous with class I for classification purposes, as it is the most common subtype. Cases were limited to children aged <20 y. Demographic, clinical, and survival data were analyzed using values grouped in categories previously defined for the SEER database by the National Cancer Institute. Duplicate cases were excluded.

All incidence data were age adjusted and normalized to the 2000 US standard population. Annual percentage change was calculated using the weighted least-squares method. Categorical variables were compared using chi-square or Fisher's exact tests as appropriate. Continuous measures were compared using student's *t*-tests. Survival curves were derived using the Kaplan–Meier method and comparisons were made using the log-rank test. SEER*Stat software, version 18.0 (National Cancer Institute; Bethesda, MD) was used to obtain incidence and survival data. All other statistical analyses were performed using SPSS, version 21.0 (IBM; Armonk, NY). Only cases with available data were included in each respective analysis. Statistical significance was determined for each analysis at alpha level 0.05.

3. Results

A total of 828 children and adolescents diagnosed with histiocytosis were identified within the data set. Overall annual incidence rate was 0.142/100,000; Table 2. This rate remained stable throughout the study period with an annual percentage change of 0.96%. Caucasian children had a higher incidence compared with African Americans, $P < 0.05$. However, children of Asian and/or Pacific Islander or Native American descent had the highest rate, 0.179/100,000 persons per annum. Children <1 y old had the highest incidence rate (0.669/100,000), followed by those aged 1–4 and 10–14 y, $P < 0.05$. Annual variations in the incidence of each histologic type are depicted in Figure 1. Boys did not have a significantly different incidence compared with girls over the study period.

Demographics and clinical characteristics of our study cohort are summarized in Table 3. The ratio of boys to girls was 1.12:1.0. Caucasian children comprised most cases (80%).