Histiocytosis X: Evidence for a Genetic Etiology

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Abstract

Histiocytosis X is a rare disorder with no particular predilection for race, age or sex. Since its discovery by Hand in 1893, the etiology has remained unknown, although viruses, bacteria and genetic factors have been implicated. Familial occurrence of this disease is very rare, and only a handful of such cases have been reported. The present study adds further evidence to support the influence of genetic factors in the etiology of histiocytosis X.

Introduction

Histiocytosis X is classified as a reticulo-endothelial disorder with varying clinical symptoms and severity. The clinical features of this disease were first described as early as 1893 by Hand [1], who believed it to be a form of tuberculosis. Lichtenstein and Jaffe [2] in 1940 identified a variation of this disorder, which they termed eosinophilic granuloma due to its characteristic intra-osseous histiocytic lesions accompanied by eosinophilic leukocyte infiltration. In 1953, Lichtenstein [3] introduced the term histiocytosis X to unify several clinical disorders that presented similar histological features. The term histiocytosis describes the proliferation of histiocytes and other inflammatory cells, and the letter “X” denotes its uncertain etiology.

The classification and nomenclature of this disorder are still somewhat debatable, due probably to the still unknown etiology. However, there exists a widely accepted classification that categorizes histiocytosis X into three separate entities. The first is the chronic disseminated form of histiocytosis X, classically known as the Hand-Schuller-Christian syndrome, characterized by a triad of symptoms which include (i) intra-osseous lesions (ii) exophthalmos and (iii) diabetes insipidus. The second is the acute or subacute form of the disease known as the Letterer-Siwe syndrome, characterized by rapid onset with widespread skeletal and extra-skeletal lesions. It occurs usually in infants less than three years of age with a severe clinical course and a sometimes fatal outcome. The third form is the most frequently reported and mildest form of the disease, with a symptom of solitary or multiple bone lesions. This variety is commonly known as eosinophilic granuloma.

Alternative classifications have been suggested, since not all cases satisfy the above criteria. Lieberman [4] proposed a simpler classification, in which eosinophilic granuloma is reclassified as a separate and distinct entity with unifocal or multifocal presentation. Therefore, Hand-Schuller-Christian syndrome may be classified as multifocal eosinophilic granuloma. Krutchkoff [5] was of the opinion that Letterer-Siwe syndrome is a separate entity altogether, and speculated that it is probably a form of malignant reticuloendotheliosis.

In an excellent review of 1,120 cases of documented histiocytosis X, Hartman [6] noted that 114, or approximately 10%, of the cases had oral involvement. Seventy-eight percent of the oral lesions were diagnosed as eosinophilic granuloma. The oral manifestation may be the earliest
sign of this disorder, which may include initial symptoms of bleeding gingiva, precocious eruption of complete dentition and ectopic eruption of permanent molars. There may also be mobility and premature exfoliation of teeth\(^7\). Radiographs of the jaw may show localized or generalized bone loss, which mimics severe periodontal disease. It may also manifest itself as erosion or ulceration of the mucosa\(^8\).

Histiocytosis X has a wide variety of clinical manifestations with varying degrees of severity. The histological picture seems to be the common denominator and is often pathognomonic. The histology is often described as an aggregation of histiocyte-like cells arranged in a sheet-like fashion superimposed with eosinophils in a fibrous connective tissue matrix. There is some evidence to suggest that these histiocytes are of Langerhans cell origin\(^9\).

**Case Report**

A 13-year-old Malay girl was referred from the Kuala Lumpur Dental Clinic, and first seen in November 1991 at the Faculty of Dentistry, University of Malaya. She presented with complaints of very loose and sometime sore teeth and a metallic taste in the mouth, especially when waking in the morning. She was the eldest of four children. Medically and developmentally, she was normal for her age.

Upon examination, it was found that she was only partially dentate (Fig. 1). Her oral hygiene was quite poor, and all erupted and partially erupted teeth were mobile (grade 2 and 3 mobility). The gingiva was generally inflamed especially around the gingival margin of the teeth. A biopsy sample was taken from the non-inflamed part of the gingiva and subsequently diagnosed as eosinophilic granuloma. An orthopantomograph revealed a partially dentate mouth, most of the upper and lower anterior teeth having been lost due to the disease process. There was extensive bilateral maxillary alveolar bone loss, giving a “floating tooth” appearance. The findings were similar in the mandible, albeit with less severe bone destruction (Fig. 2). A posteroanterior skull view showed no other cranial radiolucencies other than in the oral-maxillofacial region.

![Fig. 1](image1.png)  
The partially dentate 13-year old patient with eosinophilic granuloma.

![Fig. 2](image2.png)  
An orthopantomogram of the patient in Fig. 1, showing loose teeth with extensive alveolar bone loss.

An interview with the father of the child revealed that his third child, an 8-year-old girl, also had “loose” teeth and sore gums similar to the signs and symptoms in the elder sister. Clinical examination confirmed this finding, and revealed loosening of the lower first molars. Routine orthopantomography and posteroanterior radiography also showed the same pattern of
bone destruction, although this was not as severe as in the elder sister.

Biopsy samples taken from the mucosae of both girls gave a diagnosis of eosinophilic granuloma. At this stage it was decided to take a family history, since there was a possibility of familial occurrence of histiocytosis X. A thorough interview of the available immediate family members was done as part of the assessment. A family pedigree flowchart is demonstrated in Fig. 3.

![Pedigree Flowchart](image)

**H = The Children with Histiocytosis X**

The parental relationship in this case was a peculiar one. The eldest of the immediate family was an 81-year-old matriarch (noted on the chart). She was the grandmother of the wife (the children’s mother). However, she was also the husband’s aunt. Therefore the wife was the husband’s second niece, and hence they were genetically related. Thus inbreeding appeared to have occurred.

Further interviews with the immediate family members did not reveal any other member, past nor present, with signs or symptoms of histiocytosis X.

It was decided that a full clearance of existing teeth was necessary for the eldest daughter, since most of the teeth were beyond salvation due to extensive bone loss superimposed on periodontitis. Full upper and lower immediate dentures were then constructed, primarily for esthetic reasons. It was also decided to monitor the younger child, since her condition was not as severe as that of her elder sister.

The patient was then hospitalized and further tests were carried out, including a bone scan of the chest, pelvic region and long bones. Blood tests were also done to rule out other conditions such as cyclic neutropenia, hypophosphatasia or diabetes. A full clearance was subsequently carried out including surgical removal of unerupted second molars, and immediate dentures were then inserted. Subsequent re-lining and replacement was done as the upper and lower ridges were resorbed.

**Discussion**

The etiology of histiocytosis X is unknown, although several proposals have been put forward in the literature. These range from a viral or bacterial infection to an autoimmune reaction.

However, there have also been reported cases of familial occurrence of this disorder. The first was by Bierman [10], who reported the occurrence of histiocytosis X in a pair of twins. However, Bierman prematurely suggested a bacterial origin for the disease, and treated it with antibiotics. It may be argued that occurrence in twins does not constitute “familial” occurrence, since it represents a single pregnancy. However there are other cases in the literature of true
familial occurrence of histiocytosis X, including that reported by Miller\cite{11}, where the disorder was manifest in five siblings.

Consanguineous marriage as a factor was also reported in two cases in siblings suffering from this disorder. Falk\cite{12} reported a case where three of five children had Letterer-Siwe disease, and noted that the parents were first cousins. However the most complete and extensive evidence for familial occurrence of histiocytosis X through consanguineous marriage came from Omenn\cite{13}, who documented an extraordinarily inbred Catholic family with eight documented cases and another four from the family history, from five nuclear families.

The occurrence of histiocytosis X is quite rare in any given population\cite{6}. It is even more rare when it occurs amongst immediate family members\cite{10-12}. Armed with the fact that the marriage of the parents in the present case was consanguineous and two sisters had the same disorder, we are inclined to believe that genetics play an important role in the transmission of histiocytosis X.

Further investigations of the genetic components of this disorder proved to be futile, since there is still no specific genetic probe for detecting histiocytosis X. This is unlike proven hereditary disorders such as Huntington's chorea\cite{14}, where there is a known genetic code determining the expression of the disease in the individual.

There are, however, two possible ways by which the disorder may have been passed through the generations. One is the occurrence of a mutation in one particular generation, and the other is expression of a homozygous recessive gene in the children due to consanguineous marriage, assuming that both parents were heterozygous carriers.

It has been one hundred years since Hand initially discovered the symptoms of what is now termed histiocytosis X. The etiology and pathogenesis of this disorder continue to frustrate researchers around the world. The present case will hopefully add to what little is known about this peculiar disorder.

References