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Histiocytic disorders of children and adults: introduction to the problem, overview, historical perspective and epidemiology

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The histiocytic disorders are defined as disorders due to an abnormal accumulation of cells of the mononuclear phagocytic system (MPS), consisting of dendritic cells (DCs) and macrophages. They comprise a wide variety of diverse conditions that affect both children and adults, and have been difficult to classify and to treat.

Figure 1.1 is a simplified schematic representation of the development of various components of the MPS from the primitive CD34+ hematopoietic stem cell.

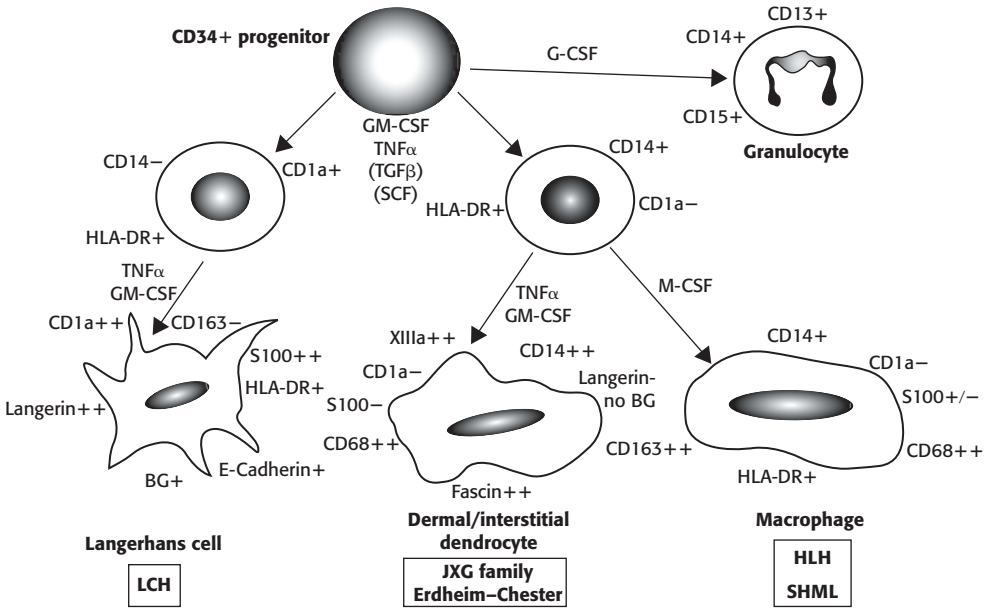

Figure 1.1 Schematic representation of histiocyte developmental pathway. Development along alternate pathways such as from monocytes or even lymphocytes has been shown to be possible; BG: Birbeck granule; GM-CSF: granulocyte–macrophage colony stimulating factor; HLA: human leukocyte antigen; JXG: juvenile xanthogranuloma; SCF: stem cell factor; TNFα: tumour necrosis factor α; TGFβ: transforming growth factor β. Reprinted with permission from John Wiley & Sons

Table 1.1 Characteristics of histiocytes in health and disease*

Clinical	LCH	Interdigitating cell sarcoma	JXG family	HLH	SHML
	LC	**IDC**	**DD**	**M/M**	**SHML**
HLA-DR	++	+	−	+	+
CD1a	++	−	−	−	−
CD14	−	−	++	++	++
CD68 (KP-1, PGM-1)	+/−	+/−	++	++	++
CD163	−	−	−	++	++
Factor XIIIa	−	−	++	−	−
Langerin	++	−	−	−	−
Fascin	−	++	++	+/−	+
S100	+	++	−	+/−	+
Lysozyme	−	−	−	++	++
Birbeck granules	+	−	−	−	−
Hemophagocytosis				+/−	
Emperipolesis					+

DD: dermal dendrocyte; HLH: hemophagocytic lymphohistiocytosis; IDC: interdigitating cell; JXG: juvenile xanthogranuloma; LC: Langerhans cell; M/M: monocyte/macrophage; SHML: sinus histoctosis with massive lymphadenopathy (SHML cellular markers overlap with dendritic and M/M markers).

*Personal communication of R. Jaffe.

It has been shown that development takes place in response to different cytokines, and that the fate of the cells can be substantially altered or skewed by changes in the cytokine microenvironment (Young, 1999). Advances in recent years have shown that although the vast majority of mononuclear phagocytes probably do stem from this myeloid hematopoietic lineage, lymphoid and mesenchymal progenitors may also give rise to mature DC and macrophages that may be indistinguishable from their myeloid counterparts. In Chapter 3, Nikolić and Leenen discuss the complex relationship between macrophages and DCs, and give evidence that they are in fact on the extremes of a spectrum. Nonetheless, classification of the histiocytic disorders according to their relationship to DCs or macrophages remains useful from a clinical standpoint.

The histiocytic disorders are generally defined by their constitutive cell, on the basis of well-established pathologic and immunohistochemical criteria (Table 1.1). It has become obvious that establishment of the correct individual diagnosis requires the fulfillment of these classic criteria, but also requires the correct clinical context. The diagnostic criteria are, therefore, correctly termed 'clinicopathologic' (Jaffe, Chapter 2).

Table 1.2 Classification of histiocytic disorder

1	**Disorders of varying biologic behavior**
	a. *Dendritic cell related*
	Langerhans cell histiocytosis
	Juvenile xanthogranuloma and related disorders including:
	– Erdheim–Chester disease
	– Solitary histiocytomas with juvenile xanthogranuloma phenotype
	Secondary dendritic cell disorders
	b. *Monocyte/macrophage related*
	Hemophagocytic lymphohistiocytosis
	Familial and sporadic
	Secondary hemophagocytic syndromes:
	– Infection associated
	– Malignancy associated
	– Autoimmune associated
	– Other
	Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)
	Solitary histiocytoma of macrophage phenotype
2	**Malignant disorders**
	Dendritic cell related
	Histiocytic sarcoma (localized or disseminated)
	Monocyte/macrophage related
	Leukemias:
	– Monocytic leukemias M5A and B
	– Acute myelomonocytic leukemia M4
	– Chronic myelomonocytic leukemias
	Extramedullary monocytic tumors or sarcoma (monocytic counterpart of granulocytic sarcoma)
	Macrophage-related histiocytic sarcoma (localized or disseminated)
	(specify phenotype: follicular dendritic cell, interdigitating dendritic cell, etc.)

Adapted from Favara *et al.* (1997).

In 1987, the Writing Group of the Histiocyte Society attempted to bring some order into the chaos surrounding these diseases, by classifying them according to their relationship to normal histiocyte subsets (Chu *et al.*, 1987). The classification was revised in 1997 (Favara *et al.*, 1997) to take into account the biologic behavior of the various disorders (Table 1.2). In this system, the major histiocytic disorders are divided into two broad groups, those of varying biologic behavior and those that are truly malignant. Within each category the disorders are subclassified according to their affiliation with DCs or with the macrophage/monocyte pathway. At present the uncommon histiocytic disorders – the non-Langerhans cell histiocytoses

(non-LCH) – are divided between the two classes, with disorders thought possibly to arise from the dermal dendrocyte, such as the juvenile xanthogranuloma family, being classified with the DC disorders, while those disorders such as sinus histiocytosis with massive lymphadenopathy (SHML) (Rosai–Dorfman disease) being assigned to the macrophage line. When dealing with such varying clinical behavior, no classification system is likely to be perfect, but the system does provide a method of standardizing the nomenclature, and giving a 'universal histiocytic language' (Egeler and D'Angio, 1998). This together with the guidelines for diagnosis and for uniform follow-up provided by the Histiocyte Society (Chapter 6) have made possible the large international cooperative studies which have shed light on the epidemiology, natural history and therapeutic outcomes of the major histiocytic disorders, LCH and hemophagocytic lymphohistiocytosis (HLH). Over the past decade, a vast amount of research has improved understanding of the basic science of normal and abnormal histiocytes, and the clinical aspects of LCH and HLH as well as the uncommon histiocytic disorders (the non-LCH).

In the following chapters, the biology, genetics, histopathology, clinical presentation, diagnosis, natural history, therapy and prognosis of the 'classic' histiocytic disorders, LCH, HLH and the non-LCH will be reviewed in depth.

Langerhans cell histiocytosis

LCH is by far the commonest of the histiocytoses, characterized by excess accumulation of CD1a+ Langerhans cells (LCs) at various tissue sites.

The disease manifests in a variety of ways, ranging from spontaneously regressing single lesions, to repeated reactivations with the risk of permanent long-term disabilities, to a life-threatening multisystem (MS) disorder with rapid progression and death.

LCH has been variously classified as a neoplasm, a reactive disorder or an aberrant immune response (Bhatia *et al.*, 1997). As will be described in later chapters, LCH cells are pathologic cells, but the granulomatous lesion includes the accumulation of normal inflammatory cells such as eosinophils, lymphocytes and macrophages. The cellular infiltration and the clinical features are all explicable as a result of aberrant secretion of cytokines by lesional cells and activated T-cells, leading to a unique clinicopathologic picture (Egeler *et al.*, 1999). Recent advances suggest that clonal changes in LCH cells underlie the aberrant immune interaction with T-cells (Laman *et al.*, 2003), nonetheless the exact etiology and pathogenesis remains uncertain. The following chapters will describe the function of normal LCs in the immune system, the large body of literature regarding pathologic LCH cells, its cytokine microenvironment, and the evidence for and against LCH being a neoplastic, genetic or infectious disorder.

Investigators in the field have long been aware that LCH in adults is at least as significant as in the pediatric population. While pediatric histiocytoses have found a base in the world of pediatric oncology, adult LCH patients have for the most part no such niche, being variously looked after by dermatologists, pulmonologists, surgeons and neurologists. Therefore this book includes chapters on adult LCH written by experts in the field, while other chapters on LCH of skin, bone, uncommon histiocytic disorders and HLH will include sections dedicated to issues specific to adult patients.

Historical aspects of LCH

In 1868, Paul Langerhans, then a 21-year-old student, published the landmark manuscript describing the non-pigmentary DCs in the epidermis which now bear his name. The sketches he made and his quantification (500–900/cm^2) are still valid today (Lampert, 1998). The first clear description of a patient with impetigo and holes in the cranium is by Smith in 1865 (Coppes-Zantinga and Egeler, 2002), although there is a description of a non-fatal disease associated with painful skull lesions by Hippocrates (about 400–450 BC) (Donadieu and Pritchard, 1999).

In 1893, Hand described a child with polyuria and exophthalmos which he attributed to tuberculosis (Hand, 1893). Schüller (1915), and Christian (1920), described similar patients with skull defects, exophthalmos and diabetes insipidus (DI), and eventually the eponym Hand–Schüller–Christian disease was given to a disease with a characteristic triad of exophthalmos, skull lesions and DI (Coppes-Zantinga and Egeler, 2002). In 1933, Siwe grouped previously reported cases (including one by Letterer in 1924) of organomegaly, lymphadenopathy, localized tumors in bone, secondary anemia, a hemorrhagic tendency and hyperplasia of non-lipid storing macrophages, into the disease that later became known as Letterer–Siwe disease (Siwe, 1933). In 1941, Farber noted that these two conditions, plus the newly diagnosed eosinophilic granuloma of bone, described the previous year in two separate articles (Lichtenstein and Jaffe, 1940; Otani and Ehrlich, 1940), represented variations of the same disease process (Farber, 1941). Later Lichtenstein introduced the concept that the three entities were part of a spectrum of the same disorder which he called histiocytosis X (Lichtenstein, 1953). In 1961, Birbeck *et al.* described the characteristic granules seen on electron microscopy (EM), thus introducing a distinctive recognition marker (Lampert, 1998) (Figure 1.2). During the next few years several investigators described the finding of Birbeck granules in different forms of LCH, and in 1973 Nezelof published a report that showed that histiocytosis X was the result of proliferation of pathologic LCs (Nezelof, 1992), a manuscript (and concept) that took many years to be accepted (Coppes-Zantinga and Egeler, 2002). In 1983, it was suggested that the name histiocytosis X be changed to Langerhans cell histiocytosis (Risdall *et al.*, 1983), in recognition of the key role of LCs in all forms of the disease (Risdall *et al.*, 1983). Finally in 1985,

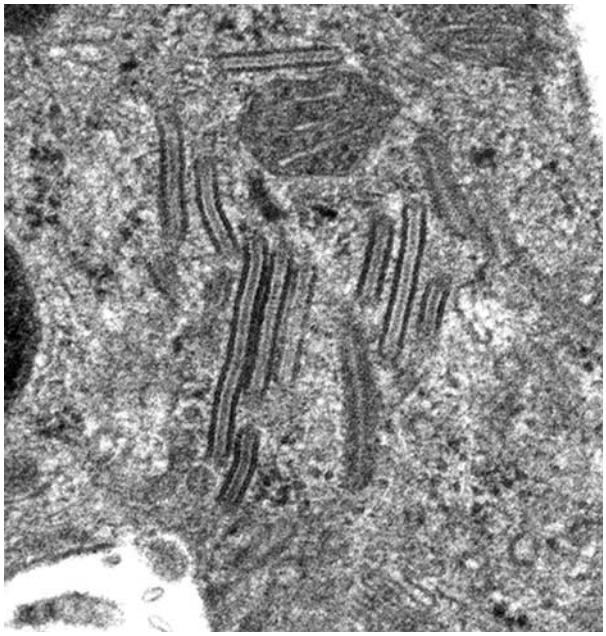

Figure 1.2 Electron microscopic view of characteristic granules as described by Birbeck *et al.* (1961)

Dr. Giulio D'Angio convened the first workshop on histiocytosis leading to the formation of the Histiocyte Society, an international society dedicated to the understanding of all aspects of the histiocytic disorders (Coppes-Zantinga and Egeler, 2002). An important step which soon followed was the formation by the Toughill family of the parent support group, now the very successful Histiocytosis Association of America, which together with similar groups from other countries, is a major supporter of research, as well as parent and patient support. Together with the 'Nikolas Symposium' an annual 'think-tank' supported by the Kontoyannis family, at which basic researchers and clinicians interested in these diseases are brought together to formulate new ideas, they have been responsible for many of the advances that have been made over the last two decades.

Epidemiology of LCH

Age and gender

LCH can present at any age from the neonatal period until old age. The estimated prevalence in children is 1:50,000 (Carstensen and Ornvold, 1993) with an annual incidence of 2–5/10^6/year in children under 15 years of age. A more recent study from Sweden, however, found a higher incidence of 8.9/10^6/year in children with the increase seen in MS as well as single system (SS) disease (Karis *et al.*, 2003).

Moreover, since 30–50% of cases occur in patients over the age of 15 years (Berry and Becton, 1984), the actual incidence figures for all age groups is probably closer to 11–12/10^6/year. These figures almost certainly underestimate the scope of the problem, as many patients, particularly those with localized bone or skin LCH, are likely to go un-referred and undiagnosed.

In one study of 346 LCH patients less than 15 years of age, the median age at diagnosis was 30.2 months (The French LCH Study Group, 1996). A slight male preponderance was reported similar to that in other studies, although some series have reported a male predominance as high as 2:1 (Carstensen and Ornvold, 1993). In the overall pediatric age range, almost 70% have SS disease of which the commonest system involved is bone (Stuurman *et al.*, 2003). However MS LCH usually occurs in children less than 2 years of age, multifocal SS in children between 2 and 5 years, while 50% of unifocal bone disease occurs in children over the age of 5 years (Huang and Arceci, 1999).

Analysis of patients over the age of 18 years, reported to the Histiocyte Society Adult Registry, showed a mean age at diagnosis of 35 with 10% being older than 55 years. Five percent of adults had a delay of more than 10 years between onset of symptoms and diagnosis. Over two-thirds (68.6%) had MS disease with skin and lung involvement in 51% and 62%, respectively (Aricò *et al.*, 2003). Of the 86 adults (31%) with SS LCH, SS bone was seen in 38%, SS skin in 14.3% and SS lung in 51%, most of whom were smokers. A more detailed discussion of adult LCH can be found in Chapters 7–10.

Genetic and ethnic factors

The only histiocytic disorder unequivocally due to an underlying genetic abnormality is familial HLH. Evidence of familial clustering of LCH and higher concordance in monozygotic twins than would be expected by chance suggest that a genetic predisposition may also exist for LCH (Aricò *et al.*, 2001).

Evaluation of 84 Nordic patients found no association between human leukocyte antigen (HLA) subtypes and the occurrence of LCH; however, stratification into SS and MS disease showed that SS patients more often had the phenotype DRB1*03 and the deduced haplotype HLA-A*01, B*08, DRB1*03 was found only in SS patients. The possibility was raised that HLA-DRB1*03 plays a protective role against developing MS disease. Further studies of this interesting concept are required (Bernstrand *et al.*, 2003). McClain *et al.* (2003) found a high incidence of DR4 or Cw7 in Caucasian LCH patients, particularly those with single bone disease and suggested possible associations with immune dysfunction leading to LCH.

The genetics of LCH and of HLH will be discussed in detail in Chapters 5 and 17.

The increased incidence reported in white children is likely to be due to reporting bias, as there is no known racial bias for the development of LCH.

Risk factors for LCH

Defective immune function has long been suggested as being central to the pathogenesis of LCH. Recent studies described in detail in Chapter 3, discuss the possibility of genetic abnormality in LC function which may underlie the immune disorder.

An alternative hypothesis is that this is a reactive disease, resulting from environmental or other triggers which lead to the aberrant reaction between LCs and T-cells (Glotzbecker *et al.*, 2002). The association between LCH and malignancy described in Chapter 14 may give some credence to this hypothesis.

Alternatively, environmental and other factors may act as initiating events on the background of immune dysregulation.

An epidemiologic study compared 459 children with LCH to matched case–controls from the normal population and to children with cancer. Risk factors associated with MS-LCH in the study (Bhatia *et al.*, 1997) were an increase in infections and use of antibiotics in the first 6 months of life and a family history of thyroid disease, while SS-LCH was significantly associated with diarrhea and vomiting in the postnatal period. Both MS and SS disease were associated with a history of thyroid disease in the proband. A history of smoking pre-conception and *in utero*, maternal infections or medication use during pregnancy, did not appear to be associated with a higher risk of LCH even in early onset MS disease. Patients with LCH were consistently under-immunized compared to controls. It is interesting to speculate that lack of immunization rendered the children more susceptible to infection leading to LCH, but the association could simply be due to deferral of immunizations in ill children (Bhatia *et al.*, 1997).

Studies for an infectious origin in LCH have produced varying results. An analysis for nine different viruses by *in situ* hybridization (ISH) and polymerase chain reaction (PCR) failed to demonstrate an association (McClain *et al.*, 1994); however, more recently human herpes virus (HHV)-6 has been found in a high percentage of LCH lesional tissue by immunohistochemistry and ISH by investigators from Philadelphia, who suggest that all the manifestations of LCH could be secondary to a viral infection of lymphocytes (Glotzbecker *et al.*, 2002). Further studies to clarify the role of HHV-6 and other viruses are necessary.

In adults, cigarette smoking has been shown to be a clear risk factor for the development of pulmonary LCH. The exact relationship of this sometimes polyclonal lung disease to the monoclonal forms of the disease remains to be elucidated, particularly in view of a Swedish study which raised the possibility of an increased risk for the development of lung LCH in adult survivors of pediatric LCH who smoke (Bernstrand *et al.*, 2000).

No other environmental risk factors for the development of LCH have been found to date.

Hemophagocytic lymphohistiocytosis

The hemophagocytic syndromes are subdivided into primary and secondary forms.

Primary HLH appears to arise *de novo* without any known preceding conditions. A major subdivision of primary HLH is the autosomal recessive form of the disease, now mainly called familial hemophagocytic lymphohistiocytosis (FHL). Recent studies suggest that 20–40% of FHL is due to perforin gene mutations (Goransdotter Ericson *et al.*, 2001) but, as discussed in Chapter 17, several gene mutations may underlie the deficiency in the triggering of apoptosis which results in the HLH phenotype. As more genetic defects are discovered, the diagnosis of non-familial primary HLH will be made correspondingly less often, and it may well be that all primary HLH will eventually be shown to have a genetic basis.

In secondary forms of HLH, hemophagocytosis occurs as a result of macrophage activation by a known stimulus which can be infectious, malignant, autoimmune or physical. A number of infections have been shown to be associated with secondary HLH, of which Epstein–Barr virus (EBV) is the commonest (discussed in detail in Chapter 18); but other viruses, bacteria and fungal infections may also be found (Fisman, 2000).

Whatever the etiology, the pathogenesis involves production of high levels of proinflammatory cytokines by T-helper cells, excessive activation of monocytes and macrophages leading to the phagocytosis of blood cells which is the hallmark of the disease (see Chapters 18 and 19).

Historical perspectives on HLH

The first publication describing FHL is usually said to be that of Farquhar and Claireaux (1952). They reported two siblings with unexplained fevers, progressive panhematopenia, hepatosplenomegaly and terminal bruising. At autopsy a proliferation of histiocytes were found, many of which showed erythrophagocytosis (Filipovich, 1997). As pointed out, however (Fisman, 2000), the syndrome also called histiocytic medullary reticulosis was first described in 1939 (Scott and Robb-Smith, 1939). In 1979, Risdall *et al.* described 19 patients with similar findings, most of whom proved to have virus-associated HLH (Risdall *et al.*, 1979). In 1980, successful treatment of two children with etoposide was described (Ambruso *et al.*, 1980); however in 1983, a review of FHL still showed a median survival of less than 2 months, and a 1-year survival close to 0% (Janke, 1983). In 1986, an important breakthrough occurred when Fischer *et al.* demonstrated that allogeneic bone marrow transplant could affect a cure in some patients (Fischer *et al.*, 1986). In 1994, the HLH-94 protocol of the Histiocyte Society was developed, combining immunotherapy with chemotherapy and recommending bone marrow transplantation for all primary HLH patients for whom a donor could be found.

Recently published results of this protocol provide unequivocal evidence of the value of international collaboration in uncommon disorders (Henter *et al.*, 2002).

This improvement in clinical management was paralleled by the rapidly increasing understanding of the underlying biology. Many studies show that the clinical syndrome was due to an excess of proinflammatory cytokines (Henter *et al.*, 1991b; Imashuku *et al.*, 1991; Osugi *et al.*, 1997), and suggested that the familial form of HLH was due to faulty triggering of apoptosis (Henter *et al.*, 1996). This led to the discovery that many of the cases were due to defects in the perforin gene (Dufourcq-Lagelouse *et al.*, 1999; Ohadi *et al.*, 1999; Stepp *et al.*, 1999), and the subsequent finding of several other gene defects which result in the same phenotype.

Epidemiology of HLH

The estimated incidence of FHL is 1/50,000 live births (Henter *et al.*, 1991a), but this figure will almost certainly increase as more genetic defects are discovered.

The male to female ratio is 1:1. There is an increased incidence of the disease in ethnic groups with higher rates of consanguinity (Henter *et al.*, 1998), and this holds true even within the same ethnic group. In Japan, FHL is significantly commoner in Western Japan where the rate of consanguinity is higher (Ishii *et al.*, 1998). The majority of patients present before the age of 1 year; however, with the finding of the perforin and other gene mutations, family members presenting with the disease in their 20s have been described.

The association of secondary HLH with EBV infection has been well described, more than 50% of the patients coming from the Far East Japan, China or Taiwan (Janke *et al.*, 1998). At least in the childhood population, EBV-associated HLH appears to occur in young children, with more than 50% being less than 3 years of age (Janke *et al.*, 1998), and with a mortality that has been estimated to be as high as 41% (Imashuku, 2000). Although a few cases of FHL present in young adults, the majority of adult cases are due to secondary HLH. A recent review from Japan, of 52 adults with HLH, showed underlying lymphomas in 26 (lymphoma-associated hemophagocytic syndrome, LAHS), virus-associated hemophagocytic syndrome (VAHS) in 17, bacterial disease in 6 and autoimmune disease (all systemic lupus erythematosus (SLE)) in 3. LAHS had the highest median age at diagnosis and the highest mortality in this study (Takahashi *et al.*, 2001), which confirmed previous reports that lymphoma is the commonest cause of adult-onset HLH.

Conclusion

After a prolonged period of inertia following the original description of LCH, the last few decades has seen major gains in knowledge regarding the underlying defects, clinical presentation, therapy and outcome of the histiocytic disorders.