Strategies for the Prevention of Central Nervous System Complications in Patients with Langerhans Cell Histiocytosis

The Problem of Neurodegenerative Syndrome

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KEYWORDS

• Langerhans cell histiocytosis • Central nervous system • Diabetes insipidus
• Neurodegenerative disease • Neuroinflammatory disease

KEY POINTS

- The syndrome of neurodegeneration-central nervous system-Langerhans cell histiocytosis (ND-CNS-LCH) in a subset of patients with LCH remains a progressive and devastating complication. Although a definitive incidence of this clinical syndrome remains unclear, estimates suggest around 10%. Patients at high risk for developing ND-CNS-LCH usually have disease involvement of the mastoid, temporal, and orbital bones as well as having developed diabetes insipidus.
- ND-CNS-LCH is usually a waxing and waning, yet progressive, disorder characterized by radiographic involvement of the cerebellar peduncles, basal ganglia, and often pons. Clinical signs and symptoms include problems with physical coordination (ataxia, dysarthria, dysmetria) as well as neurocognitive and psychological difficulties.
- The cause of ND-CNS-LCH is unknown, but seems to be in part mediated by CD8-positive lymphocytes and neuroinflammatory cytokines/chemokines. Whether ND-CNS-LCH is due to the presence of active, yet undetectable by current methods, LCH, or a paraneoplastic consequence of dendritic cell activation of the immune system to recognize CNS antigens is unknown.
- Several attempts at treatment with immunosuppressive or cytotoxic/immunosuppressive approaches have not resulted in an optimal strategy. There is a great need for prospective, randomized trials that will also measure critical biological and clinical characteristics of patients with new onset ND-CNS-LCH as well as for newly diagnosed patients with LCH at high risk for developing ND-CNS-LCH.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a myeloid precursor/dendritic-cell-related histiocytosis; approximately two-thirds of those affected are children.[1] LCH is characterized by mutations of genes of the ERK signaling pathway as well as a lesional "cytokine storm," a term referring to both the high level and the diversity of locally synthesized cytokines.[2–10] Thus, in many ways and like many other neoplastic disorders, LCH can be considered an inflammatory neoplasia, meaning that although proliferation and survival of the neoplastic cells are driven by key genetic changes, the pathophysiology of the neoplasia is modified by the interchange of the neoplastic cells with their microenvironment and vice versa. Thus, increased levels of several of a variety of cytokines/chemokines have been found in the plasma/serum of patients with active LCH, and these levels typically reflect systemic disease activity (**Table 1**).[11,12]

Central nervous system (CNS) lesions are also common in LCH. These lesions include active lesions (ie, clear involvement with lesional LCH cells) involving the hypothalamic-pituitary axis with secondary central diabetes insipidus (CDI), space-occupying lesions at other sites, and neurodegenerative (ND) lesions of the cerebellum and basal ganglia.[13,14] Patients with an increased risk for the development of CNS lesions have been defined among patients with LCH.[15,16] Besides permanent CDI, the development of ND-CNS-LCH represents the most serious late CNS sequela.[13,17–19]

One of the hypotheses regarding CNS neurodegenerative disease (NDD) is that the level of CNS lesional cytokines/chemokines at disease onset may contribute to the subsequent development of CDI and ND-CNS-LCH disease, and that this level will be reflected in the cerebrospinal fluid (CSF). This hypothesis is based on consideration of relevant studies on serum/plasma measurements reflecting systemic disease activity. To date, there are reports concerning cytologic findings in CNS-LCH[17,20];

Table 1
Cytokines/chemokines as biomarkers in patients with Langerhans cell histiocytosis

Investigated Biological Materials	Cytokines/Chemokines Involved	References
Lesional	IL-1, IL-6, M-CSF[2], GM-CSF[2], TNFα, IL-3, CD40L, RANKL-RANL CCR6-CCL20, CCR7, CCL5, CXCR3-CXCL11	7–10
Systemic (serum/plasma)	IL-1RA, TNFα, IL-1β, CD40L, RANK, RANKL, OPG, sIL-2R	11,12
CSF[1] (cerebrospinal fluid)	In active CNS disease: Presence of CD1a positive cells	20
	In cases of ND-CNS-LCH: Increased NFL, GFAP, TAU	21
	Other biomarkers at the onset of active disease in patients at high risk for CNS-LCH: IL-6, TNFα, IL-8, Opn, DcR3, sCD27, MMP-9, MMP-9/TIMP-1 ratio, RANKL-RANL, OPG, CXCL10, CXCL 11, CXCL 13, others	Needs to be studied

Abbreviations: CCL, CC chemokine ligand; CCR, CC chemokine receptor; CSF[2], colony-stimulating factor; CXCR, CXC chemokine receptor; CXCL, CXC chemokine ligand; DcR3, decoy receptor 3; GFAp, glial fibrillary acid protein; NFL, neurofilament protein light chain; OPG, osteoprotegerin; Opn, osteopontin; RANK, receptor activator of NF-κB; RANKL, RANK ligand; MMP, matrix metalloproteinase; TAU, total τ protein, ligand; TIMP, tissue inhibitor of metalloproteinases.

Data from Refs.[7–12,20,21]