



## SPECIAL ARTICLE

# Neurodegeneration in Langerhans Cell Histiocytosis: beyond a Sequela



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**Abstract** Langerhans cell histiocytosis (LCH) is a rare inflammatory myeloid neoplasm with heterogeneous organ and system involvement. Neurodegenerative LCH (ND-LCH) is an uncommon late manifestation with progressive clinical and radiological features, substantial morbidity and an unpredictable course. Historically it was considered a paraneoplastic sequela for which treatment was largely ineffective. Multisystemic disease, central diabetes and orbital and/or skull base bone lesions are risk factors associated with the development of ND-LCH. Early diagnosis, guided by clinical, radiological, electrophysiological and neurocognitive evaluations, may

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Central nervous system;  
Targeted therapy;  
BRAF inhibitors;  
MEK inhibitors;  
MAPK inhibitors

## PALABRAS CLAVE

Histiocitosis;  
Histiocitosis de células de Langerhans;  
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Sistema nervioso central;  
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Inhibidores BRAF;  
Inhibidores MEK;  
Inhibidores MAPK

enable timely treatment to halt or slow its progression. Recent identification of activating mutations in the mitogen-activated protein kinase (MAPK) pathway and the development of murine models have redefined ND-LCH as an active neuroinflammatory and neurodegenerative form of LCH, changing our understanding of its etiopathogenesis and identifying novel risk factors and targets for therapy.

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## Neurodegeneración en Histiocitosis de Células de Langerhans: más que una secuela

**Resumen** La histiocitosis de células de Langerhans (HCL) es actualmente considerada una neoplasia inflamatoria rara de origen mielóide que afecta a diferentes órganos y sistemas, de presentación clínica heterogénea. La HCL neurodegenerativa (HCL-ND) es una entidad tardía y poco frecuente, caracterizada por un cuadro clínico-radiológico progresivo que supone una importante morbilidad, con una evolución variable e impredecible. Históricamente fue considerada una secuela de probable etiología paraneoplásica, con tratamientos poco efectivos. La afectación multisistémica, la presencia de diabetes insípida central y la afectación ósea orbitaria y/o de la base de cráneo se consideran factores de riesgo asociados al desarrollo de la HCL-ND. El diagnóstico precoz, eminentemente clínico y radiológico, apoyado por estudios electrofisiológicos y neurocognitivos, permitiría un tratamiento temprano, posiblemente clave para revertir o ralentizar la evolución. En los últimos años, el descubrimiento de la presencia de mutaciones activadoras de la vía dependiente de la proteína quinasa de activación mitogénica (MAPK) y el desarrollo de modelos animales en ratón han permitido redefinir esta entidad como una forma de enfermedad activa de HCL que produce neuroinflamación y neurodegeneración, suponiendo un cambio en el conocimiento de la etiopatogenia, identificando nuevos factores de riesgo y posibles tratamientos dirigidos.

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## Introduction

Langerhans cell histiocytosis (LCH) is a rare hematological disorder of myeloid origin included in the group of histiocytic neoplasms that mainly affects the pediatric population.<sup>1,2</sup> After long years of debating whether it had a neoplastic or inflammatory etiology, evidence on clonal proliferation<sup>3</sup> and the discovery of the *BRAF*<sup>V600E</sup> mutation (valine substituted by glutamic acid at amino acid position 600 of the *Braf* proto-oncogene)<sup>4</sup>, and other mutually exclusive activating mutations of the mitogen-activated protein kinase (MAPK) pathway as causes of LCH<sup>1</sup>, have finally allowed its recognition as a myeloid neoplasm by the World Health Organization.<sup>5</sup>

The clinical spectrum of LCH is heterogenous and is currently understood thanks to advances in the knowledge of its pathophysiology, ranging from self-healing lesions to life-threatening multisystemic involvement requiring intensive care. The most frequent forms manifest with skeletal and mucocutaneous involvement. Involvement of risk organs (liver, spleen and bone marrow) carries a poorer prognosis, with higher rates of recurrence and decreased survival.<sup>6</sup> Despite advances in treatment that have achieved excellent survival rates,<sup>7</sup> relapse/reactivation continues to be a problem, even with targeted therapy, and cause long-

term morbidity, especially in the form of orthopedic and endocrine complications.

The central nervous system (CNS) can also be affected, but given the rarity and vague and heterogeneous definition, the incidence and prevalence of neurologic involvement have not been clearly established in the literature; it is estimated that 5%–10% of patients may experience CNS involvement<sup>8</sup> in two forms clearly differentiated in terms of their biology and clinical-radiologic features.

Nearly half of cases manifest as space-occupying lesions involving the hypothalamic-pituitary region, the choroid plexus, or the dura. These lesions are formed by histiocytes with the classic histopathological profile of extracranial lesions (CD1a<sup>+</sup>/CD207<sup>+</sup>). There is particular interest in patients who develop central diabetes insipidus (CDI), which occurs in approximately 12% of cases, and is already present at the time of LCH diagnosis in half of them.<sup>9–11</sup> Multi-systemic or craniofacial bone involvement, longer duration of disease activity or a greater number of reactivations are risk factors for CDI development (hazard ratios of 4.6, 1.7, 1.5 and 3.5, respectively).<sup>9</sup> Although cases with resolution of CDI have been reported,<sup>10</sup> CDI remains a lifelong sequela in nearly all patients, and may be associated with other hypothalamic-pituitary axis disorders in up to 40% of them.<sup>8,12</sup>

The second form of CNS involvement is neurodegenerative Langerhans cell histiocytosis (ND-LCH), which is examined in depth in this paper, focusing on recent advances in etiopathogenesis, diagnosis, and their treatment implications.

## Neurodegenerative Langerhans cell histiocytosis

Although overall survival in LCH is high,<sup>6</sup> a small percentage of patients develops a progressive syndrome of neurologic manifestations and radiological abnormalities. In 2018, Héritier et al., in the largest cohort study published of LCH patients, reported that 1.9% of patients developed clinical ND-LCH, defined as abnormalities in the neurological and/or neuropsychological examinations in association with characteristic MRI features. The cumulative incidence at 15 years was 1.8%–8.6%, likely underestimated, as oligosymptomatic patients may have been excluded from the analysis. The mean age at diagnosis of LCH-ND was 9.2 years, typically several years after the initial diagnosis of LCH (mean 6.5 years).<sup>11</sup>

## Recent insights into the etiopathogenesis of the disease

Until the *BRAF*<sup>V600E</sup> mutation was discovered in 2010 as a key molecular driver in the development of LCH, the etiology and the substantial clinical heterogeneity of the disease were poorly understood.<sup>4</sup> We currently know that activating MAPK pathway mutations in myeloid precursors at different stages of their differentiation correspond to the different clinical presentations: the less differentiated the precursors are, the more aggressive the disease. This pathological activation of the MAPK pathway promotes impaired dendritic cell migration (lack of CCR7 expression), resistance to apoptosis (upregulation of Bcl-xL), induction of a cell senescence program, and exhaustion of infiltrating T cells through checkpoint inhibition.<sup>13</sup>

Early reports based on the limited number of brain biopsies and post-mortem examinations showed neuronal and axonal destruction with diffuse inflammatory infiltrates mainly consisting of CD8<sup>+</sup> lymphocytes and CD68<sup>+</sup> and CD1a<sup>-</sup> microglia. This pattern differed from that observed in well-characterized extra-CNS Langerhans cell lesions. In consequence, ND-LCH was described as an immune-mediated paraneoplastic process.<sup>14</sup>

After the mutation discovery, McClain et al. re-analyzed the histological features of the CNS disease and demonstrated diffuse perivascular infiltration of CNS tissues by *BRAF*<sup>V600E</sup>-positive cells with a myeloid/monocytic phenotype (CD14<sup>+</sup>/CD33<sup>+</sup>/CD163<sup>+</sup>/P2RY12<sup>-</sup>), which changed the understanding of the etiopathogenesis of neurodegeneration by confirming the presence of tumor cells and, therefore, active disease.<sup>15</sup> This research group, based on clinical data and murine models, proposed that the etiology of LCH-ND involved circulating hematopoietic stem cells carrying the *BRAF*<sup>V600E</sup> variant able to infiltrate and proliferate in the CNS, a process also facilitated by blood-brain barrier disruption resulting from the proinflammatory environment

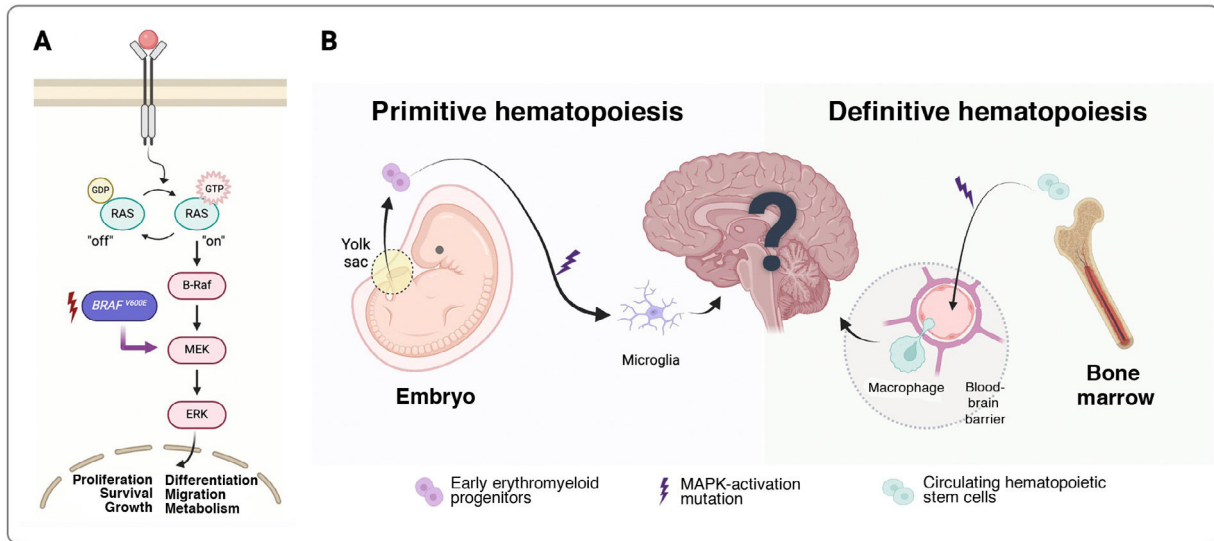
produced by these pathological cells.<sup>15,16</sup> The animal models reproduced the course of disease, with initial systemic LCH followed by neurodegeneration at a later stage. More recently, the in vitro model of Abagnale et al. supported this theory.<sup>17</sup> On the other hand, another ND-LCH murine model by Mass et al. demonstrated that the *BRAF*<sup>V600E</sup> mutation in early erythromyeloid progenitors, precursors of the future CNS tissue-resident macrophages (microglia), resulted in neuroinflammatory and neurodegenerative disease that responded to MAPK inhibitors, but without the preceding extracranial systemic involvement exhibited by most patients with LCH.<sup>18</sup> This group describes ND-LCH as a clonal neuroinflammatory disorder of microglia associated with *BRAF*<sup>V600E</sup>, suggesting the possibility of two different cellular origins of ND-LCH: microglia or bone marrow stem cells (Fig. 1). Symptoms development would depend on the duration of active disease and the size of the neurotoxic clones population.<sup>19</sup> The last statement is consistent with the recent evidence of a direct association between the hematological involvement severity and the *BRAF*<sup>V600E</sup> load detected in peripheral blood cell-free DNA analysis.<sup>7</sup>

## Risk factors for ND-LCH

Before the introduction of molecular diagnostics, clinical studies described the presence of CDI as the most significant risk factor for ND-LCH. Up to 70%–90% ND-LCH patients have CDI.<sup>20–22</sup> In turn, the risk of CDI in patients with LCH was higher among those with multisystemic involvement or involvement of orbital or skull base bone<sup>9</sup>; leading to the designation of those bone lesions as “CNS risk lesions”.

Héritier et al. found that the *BRAF*<sup>V600E</sup> mutation was significantly associated with the development of CDI and neurodegeneration, compared to patients without this variant (19.8% vs 8.4% [*P* = .006] and 6.4% vs 1.4% [*P* = .04], respectively).<sup>23</sup> This mutation has also been associated with early age at diagnosis, multisystemic disease, cutaneous and risk organ involvement, first-line therapy failure, and disease reactivation, some of which have been previously described as risk factors for CDI.<sup>9</sup> This analysis by Héritier et al., combining clinical and molecular data, showed that in the subset of patients “susceptible to clinical ND-LCH” (defined as a history of skull base/orbital bone involvement and/or CDI), the 10-year risk of clinical ND-LCH was 33.1% if *BRAF*<sup>V600E</sup> was present compared to 2.9% if it was absent (*P* = .002).<sup>11</sup>

Conventional systemic therapies commonly used to treat LCH appear to be ineffective in preventing ND-LCH. In addition, the widespread use of MAPK inhibitors in refractory or recurrent extracranial disease has raised concerns regarding their impact on long-term disease outcomes. Some groups have reported an increased incidence of clinical and radiological features of ND-LCH, with earlier onset, in patients treated with MAPK inhibitors as monotherapy.<sup>24</sup> The combination of chemotherapy and MAPK inhibitors could potentially control the systemic disease without a toxicity-related reduction in survival and prevent the increase in neurodegenerative disease observed in MAPK inhibitor monotherapy.<sup>25</sup> More experience and collaborative efforts are needed to answer these questions.



**Figure 1** Models of the etiopathogenesis of ND-LCH.

(A) Mitogen-activated protein kinase (MAPK) pathway. Growth factors/mitogens binding to tyrosine kinase receptors results in activation of Ras through phosphorylation. That results in downstream activation and homodimerization of Rafs (BRAF or ARAF) and further signaling components of MAPK. The *BRAF*<sup>V600E</sup> mutation allows BRAF to function as a monomer independently of Ras activation, promoting constitutive activation of MAPK signaling pathway. (B) Clinical studies and murine models suggest two possible pathogenic mechanisms for neurodegenerative Langerhans cell histiocytosis (ND-LCH). In the first one, a clonal population of central nervous system (CNS)-resident microglia carrying MAPK-activating mutations would proliferate (microgliosis) and release proinflammatory substances. This would lead to astrocyte activation (reactive gliosis) with neurotoxic effects, ultimately resulting in neuronal loss. The source of these activated microglia would be the early erythromyeloid progenitors, emerging from the fetal yolk sac in primitive hematopoiesis very early in embryonic development. In a second model, circulating myeloid cells carrying a MAPK-activating mutation, originating from hematopoietic stem cells in the bone marrow, migrate the CNS, where they cluster and cause neuroinflammatory damage. These cells also induce a proinflammatory state that disrupts the blood-brain barrier, facilitating further entry of this clonal population into the CNS. The likelihood of developing neurologic manifestations would depend on the size of these clonal populations within the CNS and the duration of disease.

In addition, in the era of molecular biology, the detection of *BRAF*<sup>V600E</sup> in peripheral blood at the time of diagnosis of LCH could become a useful marker in the future, not only for diagnosis and assessment of treatment response, but also to predict the development of ND-LCH.<sup>23,26</sup>

## Diagnosis of neurodegenerative disease

Neurodegenerative LCH is a syndrome characterized by progressive radiologic and clinical abnormalities. Some authors propose defining these abnormalities separately, given the poor correlation between clinical and imaging features, thus referring to "LCH-associated abnormal CNS imaging" (LACI) and "LCH-associated abnormal CNS symptoms" (LACS).<sup>27</sup>

## Neurologic and neurocognitive manifestations

Clinically, ND-LCH is characterized by a variable and progressive impairment of cerebellar (tremors, ataxia, dysmetria, dysarthria) and brainstem functions (dysphagia, cranial nerve palsy). Patients with advanced disease may develop spastic quadriplegia and pseudobulbar palsy. Several scales are available to quantify the degree of neurologic involvement. The Expanded Disability Status Scale (EDSS), widely used in multiple sclerosis and applied in LCH studies, allows objective and reproducible measurement of motor

impairment. Two scales are available to assess cerebellar impairment that can be used for diagnosis and follow-up: the International Cooperative Ataxia Rating Scale (ICARS), consisting of 19 items with a maximum possible total score of 100, and the Scale for the Assessment and Rating of Ataxia (SARA), a simpler 8-item scale with a maximum possible total score of 40. Consultation with a neurologist may be helpful in the application of these scales. The Histiocyte Society has defined an ICARS score increase of 5 or greater as indicative of clinical deterioration (diagnosis of ND-LCH).

Only a few studies have investigated the neuropsychological and cognitive changes in LCH patients.<sup>28-30</sup> Patients with CNS involvement exhibit impaired executive functioning with an impact on verbal functions, working memory, attention and processing speed. However, the clinical utility of baseline and serial evaluations has not been investigated yet, although they could contribute to early diagnosis and treatment, thereby facilitating social and school adaptation. Finally, mood disturbances and behavioral changes, which have yet to be studied in depth, have been reported in up to 25% of cases.<sup>28</sup>

## Imaging in neurodegenerative LCH

Conventional magnetic resonance imaging (MRI) is the most widely used imaging technique, although its find-

ings are nonspecific. The differential diagnosis includes conditions such as acute disseminated encephalomyelitis, metabolic and neurodegenerative diseases, chemotherapy- or radiotherapy-induced leukoencephalopathy, and paraneoplastic encephalitis.

Although the accurate incidence of LACI in the context of LCH is unknown, it is estimated that 20%–26% of patients will exhibit MRI abnormalities compatible with ND-LCH over the course of their disease.<sup>7,22,31</sup> The prevalence of LACI could increase due to targeted therapies and in the better survival of high-risk patients. Clear recommendations regarding follow-up imaging or follow-up duration have yet to be established (Fig. 2).

Infratentorial involvement predominates, with symmetrical hyperintensity in the dentate nuclei and cerebellar white matter in T2-weighted and FLAIR sequences. In advanced stages, abnormalities may extend to the cerebral peduncles, pons, and medulla oblongata. Involvement of the basal ganglia has also been reported (T1-weighted hyperintensity, with variable T2-weighted intensity), as well as patchy lesions in the supratentorial white matter (T2-weighted hyperintensity, T1-weighted hypointensity). Late-stage abnormalities include cerebellum, midbrain, and/or corpus callosum atrophy, and Virchow-Robin perivascular spaces enlargement, reflecting neuronal and axonal loss. The correlation between imaging and clinical features is limited, although up to 25% of patients with MRI abnormalities may develop clinical manifestations over time.<sup>11,27,31–33</sup>

Advanced functional imaging studies could offer greater sensitivity and specificity. Previous studies have explored techniques such as myelin or axonal content estimation, spectroscopy (N-acetyl-aspartate/creatine ratio), diffusion tensor imaging (DTI), or radioisotope-based imaging (F<sup>18</sup>-FDG PET), although further research is required to define their role in diagnosis and follow-up.<sup>34,35</sup>

### Neurophysiological evaluation

Although there is limited experience in its application, neurophysiological exams may be useful for diagnosis, follow-up and treatment evaluation response in ND-LCH. Somatosensory evoked potentials (SEPs) and brainstem auditory evoked potentials (BAEPs) have been previously analyzed in this context. Somatosensory evoked potentials may play an important role in ND-LCH early detection<sup>34</sup> and in monitoring treatment response.<sup>35</sup>

### Biochemical markers

At this moment there are no specific recommendations for cerebrospinal fluid (CSF) analysis in patients with suspected ND-LCH. Several biomarkers that could be useful for diagnosis and follow-up of these patients have been explored in research settings. For example, osteopontin<sup>15</sup> and neurofilament-light,<sup>36</sup> which are markers of inflammation and axonal damage, respectively, have been analyzed in both peripheral blood and CSF and could be useful as diagnostic and treatment response markers; however, additional prospective studies are required to help define their role in this context.

### Role of brain biopsy

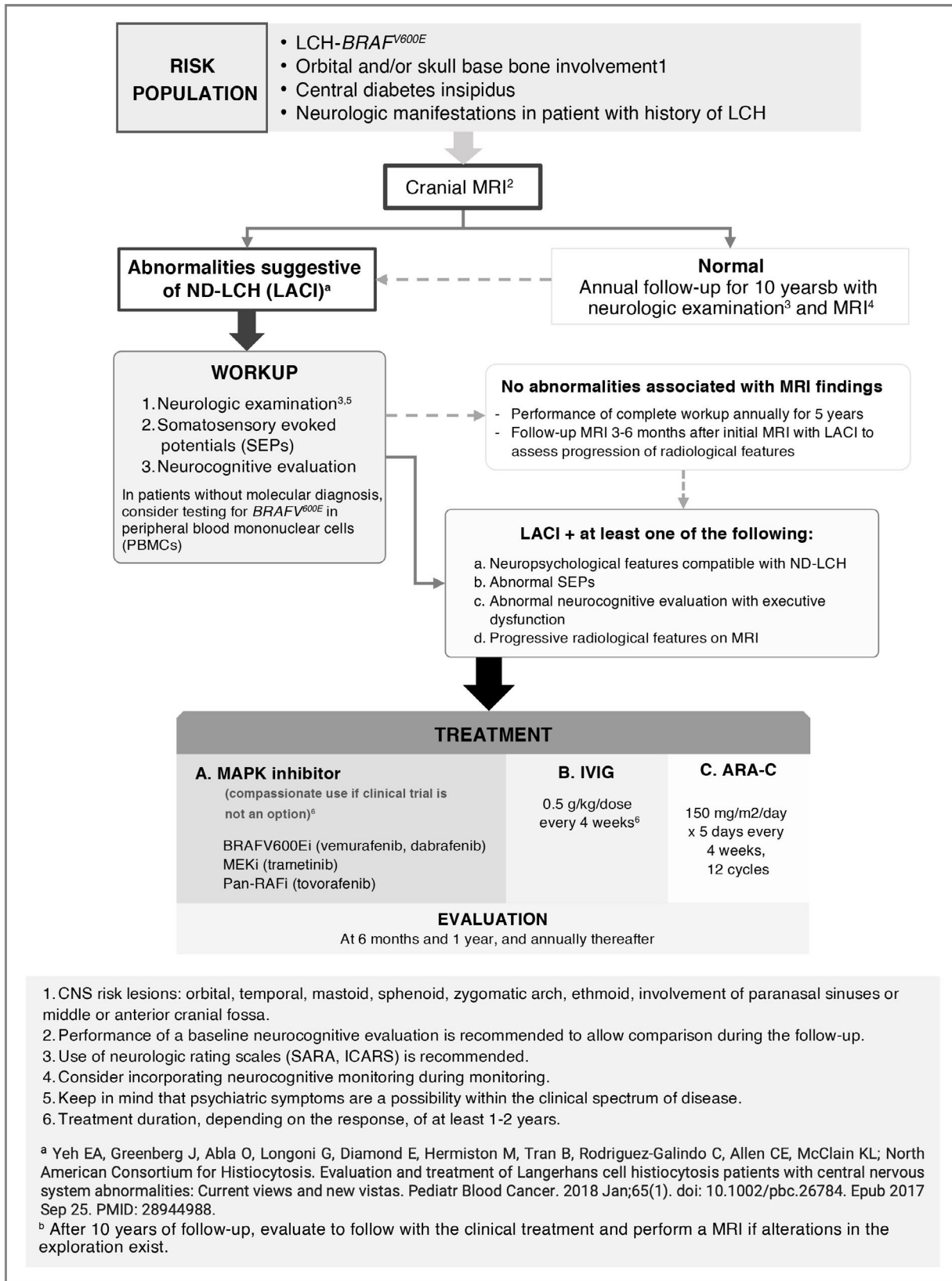
Brain biopsy is only recommended in cases in which the LCH diagnosis has not been confirmed yet and the biopsy of an alternative lesion is not feasible. Demonstrating MAPK pathway activation (through the detection of *BRAF* mutations by immunohistochemistry or molecular tests, or pERK detection by immunohistochemistry) could not only confirm the diagnosis but also reveal a potential therapeutic target, which would justify the brain biopsy procedure. Advances in neurosurgery currently allow biopsies to be performed at very complex locations with low or negligible morbidity in reference centers with appropriate expertise and technological resources. The myeloid cell markers of microglia (CD163, CD68) will be positive, but the classical stain for LCH, CD1a, will be negative.<sup>14,15</sup> On the other hand, the presence of *BRAF*<sup>V600E</sup> in peripheral blood mononuclear cells (PBMCs) as well as in the CSF has been reported in patients with radiological or clinical ND-LCH, so its detection could be used as a form of liquid biopsy.<sup>15</sup>

### Treatment

Managing ND-LCH is highly challenging, and its treatment remains complex (Table 1). Prior to the breakthrough in the understanding of LCH biology, conventional therapies (ATRA, rituximab, infliximab) at most achieved disease stabilization, reflecting the lack of knowledge about the underlying pathological mechanisms. Chemotherapy (cytarabine or clofarabine based) has been found to show clinical and radiological improvement in small series,<sup>37,38</sup> and intravenous immunoglobulin (IVIG) showed objective responses, probably due to its immunomodulator effect, so both approaches are still a recommendation today.<sup>35,39</sup>

One of the key challenges in ND-LCH management is determining the optimal timing for initiating treatment. In the pre-molecular era, early initiation was recommended because available treatments were largely ineffective at reversing the disease, and improvement was generally observed only in patients with a short disease duration. To date, some groups recommend initiating treatment in the presence of abnormal SEPs,<sup>35</sup> and neurocognitive evaluation is increasingly recognized as a relevant neuropsychological criterion. In patients who exhibit only imaging abnormalities (LACI), a conservative approach with clinical and radiological monitoring is recommended, as some may never experience progression or develop symptoms. However, in cases with radiological progression, certain groups, including the LCH-IV protocol of the Histiocyte Society (NCT02205762), suggest considering treatment initiation.

Following the molecular breakthrough, MAPK inhibitors started to be used in ND-LCH, achieving clinical or radiological improvement in up to 50%–70% of patients (Table 1).<sup>15,36</sup> The combination of chemotherapy and MAPK inhibitors, recently reported, has been found to achieve a similar response.<sup>40</sup> Despite advances in targeted therapies, patients with prolonged disease duration, who have likely experienced more extensive neuronal and axonal loss, still respond poorly. This supports the rationale for early treatment to reduce or halt inflammation and prevent subsequent damage. The duration of therapeutic effect and the risk of side



**Figure 2** Proposed approach to the screening, diagnosis and treatment of ND-LCH.

**Table 1** Treatments used in ND-LCH.

	Treatment	Number of patients (type of patient)		Response	
				Clinical	Radiological
Allen et al, 2010	Cytarabine (± vincristine)	8	(8 LACS)	4/8 RP	5/8 PR
Parekh et al, 2024	Clofarabine	8	(4 LACI, 4 LACS)	1 PR (1 LACI) 5 DS (3 LACI, 2 LACS)	
Idbaih et al, 2004	All-trans retinoic acid (ATRA)	10	(10 LACS)	10/10 DS	10/10 DS
Chohan et al, 2012	TNF $\alpha$ inhibitor (Infliximab)	1	(1 LACS)	1/1 PR	1/1 PR
Eckstein et al, 2018	Anti-CD20 monoclonal Ab (Rituximab)	8	(8 LACS)	7/8 PR	1/8 DS
Imashuku et al, 2015	IVIG + chemotherapy (Pred/VBL/MTX/6MCP)	8	(8 LACS)	1/8 PR 3/8 DS	5/8 DS
Shioda et al, 2015 <sup>a</sup>	IVIG	14	(14 LACS)	9/14 PR	ND
Trambusti et al, 2024	IVIG	11	(1 LACI, 10 LACS; all with abnormal SEPs)	7/11 PR 1/11 DS	11/11 DS
McClain et al, 2018	MAPKi (vemurafenib, dabrafenib, dabrafenib/trametinib)	4	(4 LACS)	1/4 CR 2/4 PR	3/4 PR
Eckstein et al, 2018 <sup>a</sup>	MAPKi	10	(mixed, not specified)	4/10 PR 6/10 DS	
Donadieu et al, 2018 <sup>a</sup>	MAPKi (vemurafenib)	6	(6 LACS)	1/6 PR 3/6 DS	ND
Visser et al, 2018 <sup>a</sup>	MAPKi (dabrafenib)	2	(2 LACS)	2/2 PR	2/2 PR
Santa-Maria Lopez et al, 2018 <sup>a</sup>	MAPKi (dabrafenib, trametinib)	4	(4 LACS)	2/4 PR	3/4 PR
Henter et al, 2022	MAPKi (dabrafenib, trametinib)	5	(5 LACS)	2/5 PR	3/5 PR
Henry, 2022 <sup>a</sup>	MAPKi (cobimetinib, dabrafenib)	1	(1 LACS)	1/1 PR	ND
Pegoraro et al, 2024 <sup>a</sup>	MAPKi (dabrafenib, vemurafenib, dabrafenib/trametinib, other)	33	(33 LACS)	8/15 PR 7/15 DS	ND
Karri et al, 2024	MAPKi + chemotherapy (dabrafenib, cobimetinib, dabrafenib/trametinib + Clofarabine or cytarabine)	7	(4 LACI, 3 LACS)	1/3 PR 2/3 DS	2/7 CR (2 LACI) 4/7 PR (1 LACI + 3 LACS) 1/7 DS (1 LACI)

Ab, antibody; CR, complete response; DS, disease stabilization; IVIG, intravenous immunoglobulin; LACI, LCH-associated abnormal CNS imaging; LACS, LCH-associated abnormal CNS symptoms; MAPKi, MAPK pathway inhibitor; MTX, methotrexate; ND, no data available; PR, partial response; Pred, prednisolone; SEPs, somatosensory evoked potentials; TNF, tumor necrosis factor; VBL, vinblastine; 6MCP, 6-mercaptopurine.

<sup>a</sup> Source: Annual Histiocyte Society Program and Abstract Books <https://histiocytesociety.org/Previous-Meetings-Programs>.

effects after discontinuation of these treatments remain uncertain.

Regarding treatment guidelines, large collaborative groups and expert groups have proposed standardized recommendations for follow-up and therapy (Fig. 2). The North American Consortium for Histiocytosis (NACHO) recommends treatment with cytarabine or MAPK inhibitors in patients with LACS or progressive LACI.<sup>13,27</sup> Cohen et al. pro-

vided similar recommendation, but for patients with LACI they additionally suggest neurocognitive testing to guide treatment decisions and include IVIG among the treatment options.<sup>1</sup> Preclinical studies in animal models are investigating potential novel therapies, such as CSF1R inhibitors<sup>19</sup> or Bcl-2 inhibitors (senolytic agents),<sup>16</sup> either as monotherapy or in combination with MAPK inhibitors, approaches that require further research and clinical trials.

## Conclusions

Our understanding of neurodegenerative LCH has shifted radically in recent years. It is now considered a form of active disease originating from cells located in the CNS compartment that, due to constitutive activation of the MAPK signaling pathway, drive neuroinflammation that ultimately results in neuronal and axonal loss. Central diabetes insipidus and orbital and/or skull base bone involvement remain established risk factors for ND-LCH, with the recent addition of the *BRAF*<sup>V600E</sup> mutation. Monitoring and early diagnosis of at-risk patients allow timely initiation of treatment. Although therapeutic options remain limited, MAPK inhibitors have been added to chemotherapy and immunoglobulins in the treatment armamentarium. Long-term collaborative studies are needed to support the development and implementation of novel diagnostic and therapeutic approaches for patients with ND-LCH.

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## Declaration of competing interest

The authors have no conflicts of interest to declare.

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