haematologica
Journal of the Ferrata Storti Foundation

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by Francesco Pegoraro, Irene Trambusti and Elena Sieni

Received: July 1, 2026.
Accepted: July 9, 2026.

Citation: Francesco Pegoraro, Irene Trambusti and Elena Sieni. Neurodegenerative Langerhans cell histiocytosis: building the evidence for prospective monitoring and early treatment. Response to Comment on: "Neurodegenerative Langerhans cell histiocytosis: long-term follow-up of 63 patients from the Italian Registry". Haematologica. 2026 July 16. doi: 10.3324/haematol.2026.301539 [Epub ahead of print]

Neurodegenerative Langerhans cell histiocytosis: building the evidence for prospective monitoring and early treatment.

Response to Comment on: "Neurodegenerative Langerhans cell histiocytosis: long-term follow-up of 63 patients from the Italian Registry"

Francesco Pegoraro,[1,2] Irene Trambusti,[1] Elena Sieni[1]

[1]Department of Hematology and Oncology, Meyer Children's Hospital IRCCS, Firenze, Italy; [2]Department of Experimental and Clinical Medicine, University of Firenze, Firenze, Italy

Correspondence

Elena Sieni, MD. Department of Hematology and Oncology, Meyer Children's Hospital IRCCS, Firenze, Italy. E-mail: elena.sieni@meyer.it.

Authors' contributions

Conception and design: E.S., I.T. Manuscript Writing: F.P. Manuscript revision: E.S. Research supervision: E.S. All authors contributed to the article and approved the submitted version.

Disclosure

None.

To the Editor

We thank Li and colleagues for their thoughtful comments on our study and for highlighting the clinical implications of our findings regarding the natural history and progression of neurodegenerative Langerhans cell histiocytosis (ND-LCH).[1]

As emphasized in their comment, one of the major challenges in ND-LCH remains the identification of patients at highest risk for neurological progression and the implementation of timely therapeutic interventions. Our study demonstrated that a history of LCH reactivation and radiological progression are independently associated with the development of overt neurological manifestations, supporting the concept that ND-LCH is a dynamic process that requires long-term surveillance.[2]

We fully agree that comprehensive and standardized monitoring is essential, and such an approach has been implemented at our institution for many years,[3] forming the basis of the systematic longitudinal assessments reported in our study. To further address this need, our group is coordinating an international consensus initiative promoted within the European Consortium for Histiocytosis (ECHO) network, in order to define recommendations for the evaluation and follow-up of patients at risk of or with ND-LCH. In parallel, the recently established ECHO Registry will prospectively collect clinical, radiological, neurophysiological, neuropsychological, and biological data from patients at risk of or with central nervous system involvement, providing an unprecedented opportunity to validate prognostic factors and assess outcomes in a harmonized international setting.

The authors also highlight the importance of molecular biomarkers for risk stratification and monitoring. Since the publication of our study, accumulating evidence has further strengthened the role of circulating *BRAF*^{V600E}-mutated cells as a marker of disseminated disease and long-term complications.[4] In particular, detection of *BRAF*^{V600E} in peripheral blood mononuclear cells has been confirmed as a significant risk factor for the

development of ND-LCH, supporting its incorporation into future risk-adapted surveillance strategies. Conversely, while neurofilament light chain (NfL) has emerged as a promising biomarker of ongoing neuroaxonal injury, recent data suggest that baseline NfL levels do not reliably predict ND-LCH development.[5] The integration of molecular biomarkers with imaging and clinical parameters therefore remains a major research priority for the development of robust multidimensional prediction models.

Regarding treatment, the therapeutic landscape of ND-LCH is rapidly evolving. While intravenous immunoglobulin has historically represented one of the most widely used approaches for patients with early neurodegenerative changes, its efficacy appears limited, particularly once overt neurological manifestations are established.[6] In contrast, recent evidence has demonstrated robust activity of MAPK pathway inhibitors in ND-LCH. In a large international cohort collected within the ECHO, MAPK inhibition resulted in clinical improvement in 55% of patients and radiological improvement in 74%, with disease stabilization in most of the remaining cases and a favorable safety profile.[7] Notably, none of the asymptomatic patients treated with MAPK inhibitors developed neurological symptoms during follow-up, while most showed stabilization or improvement of MRI abnormalities. These observations provide further support for the existence of a therapeutic window during the pre-symptomatic phase of ND-LCH and suggest that intervention before irreversible neuronal damage occurs may maximize long-term neurological outcomes.

Importantly, the growing evidence supporting the activity of MAPK inhibitors in ND-LCH should not be viewed solely as a treatment advance, but also as a rationale for earlier identification of patients at high risk for progression, which was one of the major contributions of our paper.[2] The availability of effective targeted therapies increases the clinical value of surveillance strategies aimed at detecting neurodegenerative involvement before the onset of overt neurological disability. Future prospective studies will be crucial

to determine the optimal timing of intervention and to identify which patients derive the greatest benefit from early treatment. In our current practice, in addition to patients with overt symptoms, we consider treatment with MAPKi in patients with ND-LCH when a combination of radiological progression (especially in the context of recurrent LCH reactivations), neurophysiological abnormalities, and elevated NfL levels is confirmed over a follow-up period of at least 6 months.

In conclusion, we appreciate the authors' interest in our work and share their view that the future management of ND-LCH will rely on the integration of standardized monitoring, molecular risk stratification, and early targeted intervention. Ongoing international collaborative efforts, including the ECHO consensus initiative and the ECHO CNS Registry, are expected to provide the prospective evidence needed to refine risk prediction and optimize therapeutic strategies for this rare but potentially devastating complication of LCH.

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