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Natural history and early intervention prognostic prediction of neurodegenerative Langerhans cell histiocytosis: insights from the Italian Registry Study. Comment on: "Neurodegenerative Langerhans cell histiocytosis: long-term follow-up of 63 patients from the Italian Registry"

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Authors' contributions

Conception and design: X.W., Z.L. and R.L. Manuscript Writing: R.L. and X.W. Manuscript revision: Z.L. and R.L. Research supervision: R.L. All authors contributed to the article and approved the submitted version.

Disclosure

The authors declare no conflict of interest.

To the Editor,

Neurodegenerative Langerhans cell histiocytosis (ND-LCH) is a highly destructive and slow progressing serious complication of Langerhans cell histiocytosis (LCH). A cohort study recently published in Haematologica, conducted by Trambusi et al., systematically revealed the natural course of ND-LCH through long-term follow-up of 63 patients in the Italian LCH registry system (RICLa) [1]. The core contribution of this study is the first clarification that disease recurrence and deterioration of cranial magnetic resonance imaging (MRI) are independent risk factors for predicting the progression of patients to overt neurological symptoms. Although there has been more understanding of the role of MAPK pathway mutations and inflammatory signals in the pathogenesis[2-4], early identification of high-risk patients, prediction of clinical deterioration, and development of standardized treatment strategies remain major challenges in the field of hematology[5]. This comment aims to explore in depth the clinical heterogeneity of ND-LCH, multidisciplinary pathways for early monitoring, and future personalized stratified treatment strategies in conjunction with cutting-edge cohort studies.

For a long time, the true incidence rate of ND-LCH is difficult to be accurately evaluated in clinical practice due to the lack of conventional imaging screening. In this retrospective study, the research team confirmed 63 cases of ND-LCH in the 637 LCH cohort, with a incidence rate of about 10%. The median time from diagnosis of LCH to the onset of neurodegenerative changes is 35 months, and up to 25% of patients do not develop symptoms until 5 years later. This remarkable long-term follow-up data echoes previous historical literature reports[6], strongly demonstrating the necessity of long-term, routine follow-up. More importantly, studies have shown that even in patients who lack traditional central nervous system high-risk factors such as

diabetes insipidus or craniofacial skeletal involvement, ND-LCH can still occur if there is a BRAFV600E mutation and a tendency towards multi system involvement. This suggests to clinical doctors that screening indications should be expanded, and follow-up monitoring should be maintained for at least 10 years.

Another highlight of this study is the use of standardized, non-invasive multidisciplinary monitoring protocols (including 3T structural MRI, neurological examination, and somatosensory/brainstem evoked potentials). This multimodal assessment successfully accurately divided ND-LCH patients into asymptomatic phase, mild impairment phase, and overt clinical symptom phase. At the beginning of diagnosis, up to 60% of patients are completely asymptomatic, and their imaging often shows mild changes. This detailed stratification provides a valuable window for observing the natural course of the disease: the vast majority of asymptomatic patients with mild baseline imaging maintain disease stability during long-term follow-up. On the contrary, patients with severe abnormalities on baseline MRI have a significantly increased risk of developing symptoms such as overt ataxia in the future.

In terms of treatment response, although this study is not a prospective intervention trial, its real-world data provides extremely critical clues for clinical decision-making. In patients with mild impairment or high-risk imaging features, early initiation of intravenous immunoglobulin (IVIG) injection can effectively curb the deterioration of the condition towards overt clinical symptoms[7]. However, once the patient crosses the boundary and enters the stage of overt symptoms, the efficacy of IVIG monotherapy is extremely limited. At this point, drugs targeting the MAPK pathway, such as BRAF inhibitor vefipronil, have shown better prospects for disease control [8, 9]. This phenomenon profoundly indicates that there is a critical "time window" for the

treatment of ND-LCH - that is, early intervention must be carried out before irreversible neuronal degeneration and loss occur[5].

Most importantly, multivariate Cox regression analysis ultimately determined that the history of LCH recurrence and the deterioration of cranial MRI lesions during follow-up were independent risk factors for predicting the progression of overt neurodegenerative disease. This confirms the close relationship between the systemic disease activity (frequent recurrence) of LCH and permanent sequelae of the central nervous system[10]. This lays a solid foundation for personalized clinical management in the future: for patients with a history of frequent recurrence, severe baseline imaging, or imaging indications of sustained progression, more rigorous follow-up frequency should be adopted and early treatment intervention should be considered. In summary, this study provides solid evidence for a comprehensive understanding of the heterogeneous natural course of ND-LCH. Future research directions should focus on integrating the aforementioned imaging indicators with emerging liquid biopsy biomarkers, such as cerebrospinal fluid neurofilament light chain protein NFL titers, to construct a multidimensional risk prediction model [9]. At the same time, there is an urgent need to conduct international multicenter prospective clinical trials to further establish the precise therapeutic and protective effects of MAPK pathway inhibitors at different stages of the disease.

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