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Neurological perspective on autoimmune activation syndrome: Exploring the immunological mechanisms underlying Hodgkin's Lymphoma

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Abstract
Hodgkin's lymphoma is a malignancy characterized by the clonal proliferation of Reed-Sternberg cells, often accompanied by systemic immune dysregulation. Recent evidence suggests that autoimmune activation may play a critical role in modulating neurological function in affected patients, yet the underlying immunological mechanisms remain poorly understood. This study aimed to investigate the interplay between autoimmune activation and neurological manifestations in individuals diagnosed with Hodgkin's lymphoma, with a particular focus on cytokine-mediated pathways and neuroinflammatory responses. A cohort of 68 patients with confirmed Hodgkin's lymphoma underwent comprehensive immunophenotyping, including quantification of circulating autoantibodies, pro-inflammatory cytokines, and T-cell subset profiling. Neurological assessment incorporated both standardized cognitive testing and neuroimaging markers of inflammation. Our findings revealed elevated levels of autoreactive antibodies and a skewed Th17/Treg balance in patients exhibiting cognitive and sensory disturbances. Notably, increased concentrations of interleukin-6 and tumor necrosis factor-alpha correlated with markers of neuroinflammation, suggesting a mechanistic link between systemic autoimmunity and central nervous system dysfunction. Furthermore, multivariate analysis indicated that the severity of neurological symptoms was significantly associated with specific immunological profiles, independent of disease stage or treatment status. These results support the hypothesis that autoimmune activation contributes to the pathophysiology of neurological complications in Hodgkin's lymphoma through targeted cytokine signalling and disruption of immune homeostasis. Understanding these mechanisms may inform the development of novel immunomodulatory therapies aimed at mitigating neuroimmune sequelae in lymphoma patients.

Keywords: Hodgkin's lymphoma, autoimmune activation, neuroinflammation, cytokines, T-cell dysregulation, neuroimmune interactions, cognitive dysfunction

Introduction

Hodgkin's lymphoma (HL) is a distinct type of lymphoid malignancy that primarily arises from B lymphocytes and is characterized by the presence of the pathognomonic Reed-Sternberg cells within affected lymphoid tissues. Although HL is relatively rare compared to non-Hodgkin lymphomas, its unique clinical, immunological, and pathological features have drawn considerable attention in both oncological and immunological research. Advances in diagnostic imaging, immunohistochemistry, and molecular profiling have significantly improved the understanding of HL, yet the complex interactions between the malignant cells and the host immune system remain incompletely elucidated. Among these interactions, autoimmune activation has emerged as a potentially critical factor influencing both systemic disease progression and secondary complications, particularly those affecting the central nervous system (CNS).

Autoimmune activation refers to a pathological process in which the immune system mounts a response against self-antigens, leading to tissue injury and dysregulated inflammatory signaling. In the context of HL, autoimmune phenomena can manifest as paraneoplastic syndromes, cytopenias, or neurological complications, often preceding or coinciding with the diagnosis of the lymphoma. The immunopathology of HL is inherently complex: Reed-Sternberg cells secrete an array of cytokines and chemokines, including interleukin-5, interleukin-6, and tumor necrosis factor-alpha, which not only promote local tumor growth but also modulate systemic immune responses. These secreted factors can skew T-cell populations, promote regulatory T-cell expansion, and facilitate the persistence of autoreactive lymphocytes, collectively creating an environment conducive to autoimmune activation. Such immune dysregulation has been implicated in various neurological manifestations observed in HL patients, ranging from cognitive impairment and peripheral neuropathies to rare central neuroinflammatory syndromes.

The neurological involvement in HL is an area of growing clinical concern. Although direct CNS infiltration by Hodgkin's lymphoma cells is uncommon, patients frequently exhibit neurological symptoms that cannot be explained by tumor burden alone. These manifestations are increasingly attributed to immune-mediated mechanisms, including autoantibody production, cytokine-induced neuroinflammation, and disruption of the blood-brain barrier. For instance, pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha have been shown to alter neuronal function, modulate glial activity, and induce neurotoxic pathways. Furthermore, the imbalance between Th17 cells and regulatory T cells, a hallmark of autoimmune activation, has been associated with both systemic inflammation and CNS involvement. Understanding these immune-mediated processes is critical, as they not only affect patient quality of life but may also influence treatment response and prognosis.

Despite mounting evidence of neuroimmune interactions in HL, the precise mechanisms linking autoimmune activation to neurological dysfunction remain poorly defined. Previous

studies have primarily focused on systemic immune abnormalities or individual neurological manifestations in isolation, often lacking integrative analysis that connects immunological markers to functional neurological outcomes. Moreover, while standard HL therapies, such as chemotherapy and immunotherapy, are effective in targeting malignant cells, they may inadvertently exacerbate autoimmune processes or mask subtle neuroinflammatory signals. This knowledge gap underscores the need for a comprehensive investigation into the immunological underpinnings of neurological complications in HL, with a particular emphasis on cytokine signaling, autoreactive antibody production, and T-cell dysregulation.

The significance of studying autoimmune activation in HL extends beyond understanding disease pathophysiology. Clinically, early identification of immune-mediated neurological complications could facilitate timely interventions and improve patient outcomes. For example, immune-modulating therapies targeting specific cytokine pathways or T-cell subsets may provide a novel approach to mitigating neuroimmune sequelae while preserving antitumor efficacy. Additionally, immunological profiling of HL patients could inform personalized treatment strategies, helping to predict which individuals are at higher risk of neurological involvement or adverse autoimmune reactions. From a research perspective, exploring the neuroimmunological interface in HL may yield broader insights into the mechanisms of paraneoplastic syndromes, systemic autoimmunity, and cytokine-mediated neuroinflammation, which are relevant to multiple malignancies and autoimmune disorders.

This study aims to bridge the gap between immunology and neurology by systematically investigating the relationship between autoimmune activation and neurological dysfunction in Hodgkin's lymphoma. Specifically, it focuses on identifying immunological signatures—such as autoantibody profiles, cytokine concentrations, and T-cell imbalances—that correlate with cognitive and sensory abnormalities in affected patients. By integrating clinical neurological assessments with comprehensive immunophenotyping, this research seeks to elucidate the mechanisms by which systemic autoimmune responses influence central nervous system function. The findings are expected to enhance the understanding of HL pathogenesis, clarify the role of autoimmunity in neurological complications, and provide a foundation for future therapeutic strategies targeting immune-mediated neurological sequelae.

In summary, Hodgkin's lymphoma represents a model disease in which malignancy, systemic immune dysregulation, and neurological complications intersect. The interplay between Reed-Sternberg cell biology, cytokine-mediated inflammation, and autoimmune activation highlights the complexity of HL beyond its hematological presentation. Investigating these mechanisms is both scientifically and clinically relevant, offering the potential to improve patient outcomes through more precise diagnosis, risk stratification, and immunomodulatory treatment approaches. By exploring the immunological mechanisms underlying autoimmune activation in HL, this study contributes to a growing body of knowledge at the interface of oncology, immunology, and neurology, ultimately aiming to enhance both our understanding and management of this multifaceted disease.

Methods

Study Design

This study employed a mixed-methods observational design integrating quantitative immunological assessments with clinical neurological evaluations to investigate the relationship between autoimmune activation and neurological manifestations in patients with Hodgkin's lymphoma (HL). The mixed-method approach was chosen to provide a comprehensive understanding of both objective immunological markers and patient-centered neurological outcomes, enabling the identification of mechanistic links between systemic autoimmunity and central nervous system (CNS) dysfunction. Quantitative analyses focused on cytokine profiling, autoantibody detection, and T-cell subset characterization, while qualitative components included structured neurological assessments and patient-reported symptom inventories.

Study Population

The study cohort consisted of 68 adult patients diagnosed with classical Hodgkin's lymphoma, recruited from two tertiary oncology centers over a 24-month period. Inclusion criteria required patients to have histologically confirmed HL, no prior history of neurological disease unrelated to HL, and willingness to undergo immunological and neurological testing. Exclusion criteria included active systemic infections, concurrent autoimmune disorders unrelated to lymphoma, and ongoing treatment with immunosuppressive agents beyond standard HL therapy. A control group of 40 age- and sex-matched healthy individuals without a history of malignancy or autoimmune disease was also recruited to provide baseline immunological and neurological parameters.

Ethical Considerations

The study protocol was approved by the institutional review boards of both participating centers, and all participants provided written informed consent prior to enrollment. Confidentiality of patient data was maintained through anonymized coding and secure data storage. Participants were informed of potential risks associated with blood sampling, neuroimaging, and cognitive testing, and were allowed to withdraw from the study at any time without affecting their standard clinical care.

Immunological Assessment

Immunological profiling was conducted through a combination of peripheral blood analysis and serum-based assays. Approximately 20 mL of peripheral blood was collected from each participant under sterile conditions. Peripheral blood mononuclear cells (PBMCs) were isolated using density-gradient centrifugation for flow cytometric analysis. T-cell subsets, including CD4+, CD8+, Th17, and regulatory T cells (Tregs), were quantified using fluorophore-conjugated monoclonal antibodies and a standardized gating strategy.

Serum samples were analyzed for pro-inflammatory and anti-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-10 (IL-10), using enzyme-linked immunosorbent assays (ELISA). Autoantibody profiles, including anti-neuronal antibodies and antinuclear antibodies (ANA), were assessed through indirect immunofluorescence and confirmed by immunoblotting for

specificity. All assays were performed in duplicate to ensure reliability, and inter-assay variability was controlled by including internal quality standards.

Neurological Evaluation

Neurological assessment was performed by board-certified neurologists blinded to the immunological results. Evaluations included both clinical and cognitive components. Clinical neurological examinations assessed cranial nerve function, motor strength, reflexes, sensory modalities, coordination, and gait. Cognitive function was evaluated using standardized neuropsychological tests, including the Mini-Mental State Examination (MMSE), Trail Making Test, and Digit Span Test, to capture attention, memory, and executive function domains.

In addition, structural and functional neuroimaging was conducted in a subset of 32 patients using 3T magnetic resonance imaging (MRI) scanners. Imaging protocols included T1- and T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR), and diffusion tensor imaging (DTI) to detect subtle neuroinflammatory changes, white matter integrity, and microstructural abnormalities. Imaging analyses were conducted by neuroradiologists using automated segmentation and volumetric software, with emphasis on regions implicated in autoimmune and inflammatory processes, such as the hippocampus, thalamus, and prefrontal cortex.

Data Collection and Standardization

Demographic and clinical data were collected for all participants, including age, sex, disease stage, treatment history, and comorbidities. Blood samples were collected at a standardized time of day (morning, fasting state) to minimize diurnal variation in cytokine levels. Neurological assessments were conducted in quiet, controlled environments to reduce confounding factors such as fatigue or external distractions. Data from immunological assays and neuropsychological tests were entered into a secure database and cross-verified for accuracy by two independent researchers.

Statistical Analysis

Data analysis was performed using statistical software (SPSS v28.0, IBM). Continuous variables, including cytokine concentrations and neuropsychological scores, were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on normality, assessed by the Shapiro-Wilk test. Categorical variables were summarized as counts and percentages. Between-group comparisons (HL patients vs. healthy controls) were conducted using independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

Correlations between immunological markers and neurological outcomes were assessed using Pearson or Spearman correlation coefficients as appropriate. Multivariate linear and logistic regression models were constructed to evaluate the association between cytokine levels, T-cell subsets, autoantibody titers, and neurological symptom severity, controlling for potential confounders such as age, sex, disease stage, and treatment status. Adjusted p-values <0.05 were considered statistically significant.

Quality Control and Reliability

To ensure reliability and reproducibility, all immunological assays were performed in a CLIA-certified laboratory with standardized operating procedures. Flow cytometry data were analyzed independently by two immunologists, and discrepancies exceeding 5% were resolved through consensus review. Neuropsychological testing was administered by trained personnel following standardized protocols, and test-retest reliability was confirmed in a random subset of 12 participants. MRI scans were reviewed by two neuroradiologists, with inter-rater agreement calculated using Cohen's kappa coefficient.

Study Limitations and Mitigation Strategies

Recognizing potential limitations inherent to observational studies, several strategies were implemented to reduce bias. Selection bias was minimized by recruiting consecutive eligible patients from multiple centers. Confounding variables, including prior treatment regimens and comorbidities, were controlled in multivariate analyses. While cross-sectional in nature, the study design included a subset of patients for longitudinal follow-up at six months to assess the temporal stability of immunological and neurological parameters. Missing data were addressed using multiple imputation methods to preserve statistical power without introducing systematic bias.

Ethical and Safety Considerations

Participants were monitored for adverse events related to blood collection, neuroimaging, or cognitive testing. Any clinically significant neurological findings were communicated to treating physicians for appropriate management. All study procedures adhered to the Declaration of Helsinki and institutional guidelines for research involving human subjects.

Summary of Methods

In summary, this study employed a mixed-methods design integrating immunological profiling with comprehensive neurological assessment to elucidate the relationship between autoimmune activation and CNS dysfunction in Hodgkin's lymphoma. By combining quantitative laboratory assays, structured cognitive testing, and neuroimaging, the study aimed to identify mechanistic links between systemic autoimmunity and neurological outcomes. Robust statistical analyses, stringent quality control measures, and careful ethical oversight ensured that the results are reliable, reproducible, and clinically meaningful.

Results

Participant Characteristics

A total of 68 patients with classical Hodgkin's lymphoma (HL) and 40 healthy control participants were included in the study. The mean age of the HL cohort was 38.6 ± 12.4 years, with 40 males (58.8%) and 28 females (41.2%). Disease staging at the time of enrollment was distributed as follows: Stage I, 12 patients (17.6%); Stage II, 28 patients (41.2%); Stage III, 18 patients (26.5%); and Stage IV, 10 patients (14.7%). The median time since diagnosis was 5.3 months (range: 1–18 months). Healthy controls had a mean age of 36.9 ± 11.8 years and a similar sex distribution (22 males, 18 females). There were no significant differences between the HL and control groups in age or sex ($p > 0.05$).

Immunological Findings

Peripheral Blood T-Cell Subsets

Flow cytometric analysis revealed significant alterations in T-cell populations among HL patients compared to controls. The proportion of CD4+ T cells was reduced in HL patients (mean 34.5 ± 8.2%) relative to controls (42.7 ± 7.5%, $p < 0.001$), while CD8+ T-cell frequencies were modestly increased (HL: 29.1 ± 6.8%; controls: 25.4 ± 5.9%, $p = 0.02$). Th17 cells were significantly elevated in HL patients (5.8 ± 2.1%) compared to controls (2.6 ± 1.2%, $p < 0.001$). Conversely, regulatory T cells (Tregs, CD4+CD25+FoxP3+) were also increased in HL patients (9.4 ± 3.1%) relative to controls (6.7 ± 2.5%, $p < 0.001$). The resulting Th17/Treg ratio was 0.62 ± 0.18 in HL patients versus 0.39 ± 0.14 in controls ($p < 0.001$), indicating a skewed balance favoring pro-inflammatory activity.

Cytokine Profiling

Serum cytokine analysis demonstrated marked elevations in pro-inflammatory cytokines among HL patients. Mean interleukin-6 (IL-6) levels were 14.8 ± 5.6 pg/mL in HL patients compared to 4.7 ± 2.1 pg/mL in controls ($p < 0.001$). Tumor necrosis factor-alpha (TNF-α) concentrations were similarly elevated (HL: 18.6 ± 6.4 pg/mL; controls: 7.9 ± 3.2 pg/mL; $p < 0.001$). Interleukin-17 (IL-17) levels were significantly higher in HL patients (9.2 ± 3.5 pg/mL) than in controls (3.4 ± 1.7 pg/mL, $p < 0.001$). Anti-inflammatory cytokine interleukin-10 (IL-10) was moderately elevated in HL patients (5.1 ± 2.3 pg/mL) compared to controls (3.7 ± 1.5 pg/mL, $p = 0.004$).

Autoantibody Profiles

Indirect immunofluorescence and immunoblotting detected the presence of autoreactive antibodies in 29 of 68 HL patients (42.6%). Anti-neuronal antibodies were present in 18 patients (26.5%), while antinuclear antibodies (ANA) were detected in 21 patients (30.9%). In contrast, only 2 of 40 healthy controls (5%) tested positive for any autoantibody, indicating a significant difference between groups ($p < 0.001$). Titers of anti-neuronal antibodies ranged from 1:80 to 1:320, with a mean of 1:145 ± 45, whereas ANA titers ranged from 1:40 to 1:160 (mean 1:92 ± 28).

Neurological Assessments

Clinical Neurological Examination

Neurological examination revealed abnormalities in 23 of 68 HL patients (33.8%). Common findings included mild sensory deficits in the distal extremities (n = 12), diminished deep tendon reflexes (n = 9), and subtle motor weakness (n = 7). No participants exhibited overt cranial nerve deficits or gross motor impairment. In contrast, all healthy controls exhibited normal neurological examination findings.

Cognitive Testing

Standardized neuropsychological assessments indicated significant cognitive impairment in HL patients relative to controls. Mean Mini-Mental State Examination (MMSE) scores were 26.8 ± 2.3 in HL patients compared to 29.1 ± 1.0 in controls ($p < 0.001$). Trail Making Test Part A and Part B completion times were significantly longer in HL patients (A: 49.2 ± 12.1 s vs. 36.7 ± 9.3 s, $p < 0.001$; B: 124.5 ± 28.6 s vs. 91.8 ± 21.7 s, $p < 0.001$), indicating deficits in attention, processing speed, and executive function. Digit Span forward and backward scores were lower in HL patients (Forward: 6.1 ± 1.2 vs. 7.3 ± 1.0, $p < 0.001$; Backward: 4.1 ± 0.9 vs. 5.2 ± 0.7, $p < 0.001$).

Neuroimaging Findings

MRI analysis of the subset of 32 HL patients revealed structural and microstructural changes consistent with neuroinflammation. FLAIR sequences demonstrated hyperintense signals in periventricular and subcortical white matter regions in 11 patients (34.4%). Diffusion tensor imaging (DTI) revealed reduced fractional anisotropy in the hippocampus and prefrontal cortex in 9 patients (28.1%) relative to age-matched control data. No gross mass lesions or direct CNS involvement by lymphoma were observed.

Correlation of Immunological Markers with Neurological Parameters

Bivariate correlation analyses indicated significant associations between systemic immunological markers and neurological outcomes. IL-6 levels demonstrated a negative correlation with MMSE scores ($r = -0.52$, $p < 0.001$) and a positive correlation with Trail Making Test Part B completion time ($r = 0.47$, $p = 0.002$). TNF-α levels also negatively correlated with Digit Span backward scores ($r = -0.41$, $p = 0.006$). Elevated Th17/Treg ratios were associated with increased incidence of sensory deficits ($r = 0.45$, $p = 0.003$) and lower MMSE scores ($r = -0.38$, $p = 0.01$). Presence of anti-neuronal antibodies correlated with prolonged Trail Making Test Part B times ($r = 0.42$, $p = 0.005$) and increased white matter hyperintensity on MRI ($r = 0.36$, $p = 0.02$).

Multivariate Analysis

Multivariate linear regression models were constructed to assess the independent contributions of immunological markers to cognitive performance, controlling for age, sex, and disease stage. IL-6 ($\beta = -0.38$, $p = 0.004$), Th17/Treg ratio ($\beta = -0.31$, $p = 0.01$), and anti-neuronal antibody titers ($\beta = -0.29$, $p = 0.02$) emerged as significant predictors of reduced MMSE scores. Logistic regression indicated that elevated IL-6 (>12 pg/mL) and positive anti-neuronal antibodies independently increased the likelihood of clinical neurological abnormalities (odds ratio = 4.2, 95% CI: 1.7–10.5, $p = 0.002$).

Summary of Key Findings

In summary, patients with HL exhibited significant immunological dysregulation, including elevated pro-inflammatory cytokines, increased Th17/Treg ratios, and the presence of autoreactive antibodies. Neurological assessments revealed cognitive deficits, subtle sensory and motor abnormalities, and imaging evidence of neuroinflammation in a subset of patients. Correlation and multivariate analyses demonstrated statistically significant associations between specific immunological markers and neurological outcomes, supporting a link between autoimmune activation and CNS dysfunction in HL.

The present study investigated the relationship between autoimmune activation and neurological dysfunction in patients with Hodgkin's lymphoma (HL), employing a mixed-methods approach that integrated immunological profiling, clinical neurological assessments, and neuroimaging. Our findings indicate that HL is associated

with systemic immune dysregulation, characterized by elevated pro-inflammatory cytokines, increased Th17/Treg ratios, and the presence of autoreactive antibodies, all of which correlate with measurable neurological impairments. These results provide compelling evidence that autoimmune activation is a significant contributor to central nervous system (CNS) dysfunction in HL, even in the absence of direct neoplastic infiltration.

Immune Dysregulation in Hodgkin's Lymphoma

The immunological findings in this study are consistent with prior reports that HL is accompanied by profound alterations in T-cell populations and cytokine networks. Specifically, the reduction in CD4+ T cells and relative expansion of CD8+ T cells observed in our cohort is reflective of a disrupted adaptive immune balance. The elevated Th17 cell fraction and concomitant increase in Tregs suggest a complex immunoregulatory milieu in which pro-inflammatory pathways coexist with compensatory regulatory mechanisms. The increased Th17/Treg ratio observed in HL patients, relative to healthy controls, is particularly noteworthy, as it implies a tilt toward inflammatory signaling despite the presence of regulatory populations. Th17 cells are known to mediate tissue inflammation through the secretion of interleukin-17 (IL-17) and recruitment of neutrophils, whereas Tregs typically suppress autoreactive responses. The coexistence of these populations in HL may contribute to systemic autoimmunity and facilitate the emergence of neurological manifestations.

Elevated circulating cytokines further corroborate the presence of systemic inflammation. IL-6 and TNF-α levels were markedly higher in HL patients, reflecting both tumor-driven immune activation and host inflammatory responses. IL-6, in particular, is a pleiotropic cytokine with roles in B-cell proliferation, T-cell differentiation, and induction of acute-phase proteins. Its correlation with cognitive deficits, as demonstrated in our correlation and multivariate analyses, supports the hypothesis that cytokine-mediated neuroinflammation may underlie the cognitive impairments observed in HL patients. TNF-α, another key pro-inflammatory mediator, is known to disrupt neuronal function, promote microglial activation, and compromise blood-brain barrier integrity, which may explain the subtle motor and sensory deficits identified in our cohort.

The detection of autoantibodies, including anti-neuronal antibodies and antinuclear antibodies (ANA), in a substantial proportion of HL patients further emphasizes the role of autoimmune activation. Anti-neuronal antibodies have been implicated in paraneoplastic neurological syndromes and may directly interfere with neuronal signaling or induce neuroinflammatory cascades. In our study, the presence and titers of these antibodies correlated with white matter hyperintensities on MRI and with impaired cognitive performance, suggesting a mechanistic link between humoral autoimmunity and CNS dysfunction.

Neurological Implications of Autoimmune Activation

Neurological evaluation revealed that HL patients exhibit both subtle and measurable impairments, including cognitive deficits, mild sensory abnormalities, and reduced executive function. The significant reductions in MMSE and Digit Span scores, along with prolonged Trail Making Test completion times, indicate that attention, working memory, and processing speed are particularly vulnerable. These findings are consistent with prior literature documenting cognitive impairment in hematologic malignancies, often described as "chemo-brain" when post-treatment, but our study highlights that such deficits can manifest even prior to extensive therapy, implicating immune-mediated mechanisms rather than treatment toxicity alone.

Neuroimaging findings in a subset of patients provided further evidence of CNS involvement. FLAIR hyperintensities in periventricular and subcortical regions, along with DTI evidence of reduced fractional anisotropy in the hippocampus and prefrontal cortex, indicate subtle microstructural changes. These regions are critical for memory, attention, and executive function, and their involvement aligns with the observed neuropsychological deficits. Importantly, no direct neoplastic CNS infiltration was detected, suggesting that immune-mediated inflammation rather than tumor invasion is the primary driver of these changes.

The observed correlations between immunological markers and neurological outcomes strengthen the proposed mechanistic link. Higher IL-6 and TNF-α levels were associated with poorer cognitive performance, while elevated Th17/Treg ratios and anti-neuronal antibody titers correlated with both clinical neurological deficits and imaging abnormalities. These associations persisted in multivariate analyses controlling for age, sex, and disease stage, indicating that immune activation exerts an independent effect on CNS function. Collectively, these findings support a model in which HL-associated immune dysregulation contributes to CNS dysfunction through a combination of cytokine-mediated neuroinflammation, autoreactive antibody activity, and T-cell-mediated effects.

Potential Mechanisms of CNS Dysfunction in HL

Several mechanisms may account for the observed neurological manifestations. First, systemic cytokine elevation may promote neuroinflammation by crossing the blood-brain barrier or inducing endothelial activation. IL-6, in particular, has been shown to modulate synaptic plasticity, alter neurogenesis, and impair cognitive processing. TNF-α can induce neuronal apoptosis, astrocytic activation, and microglial proliferation, leading to diffuse neuroinflammatory changes. Second, autoreactive antibodies may bind neuronal antigens, interfere with synaptic transmission, or trigger complement-mediated cytotoxicity. Anti-neuronal antibodies detected in our HL cohort are consistent with paraneoplastic processes that target both central and peripheral nervous structures. Third, imbalances in T-cell populations, particularly the relative increase in Th17 cells, may promote inflammation through direct infiltration of perivascular spaces or modulation of glial activity. The concomitant elevation of Tregs may reflect an incomplete compensatory response, insufficient to fully suppress autoreactive processes.

Clinical Implications

The findings of this study carry significant clinical implications. Early recognition of autoimmune-mediated neurological complications in HL could inform both diagnostic evaluation and treatment strategies. For instance, monitoring cytokine profiles, T-cell subsets, and autoantibody titers may help identify patients at elevated risk for cognitive or sensory deficits. Interventions targeting specific immune pathways, such as IL-6 blockade or

modulation of Th17 activity, may have therapeutic potential to mitigate neuroinflammation without compromising antitumor efficacy. Moreover, these results suggest that neurological assessment should be incorporated into routine HL management, even in the absence of overt neurological complaints, to identify subclinical deficits that may impact quality of life.

Strengths and Limitations

This study's strengths include its integrative methodology, combining immunological assays, standardized neuropsychological testing, and advanced neuroimaging, which allowed for a multidimensional assessment of the relationship between autoimmunity and CNS dysfunction. The use of age- and sex-matched healthy controls strengthened comparative analyses, and multivariate modeling helped control for potential confounders.

However, several limitations must be acknowledged. The cross-sectional design limits causal inference, and longitudinal studies are required to determine whether immune-mediated neurological changes progress over time or respond to HL treatment. Sample size, particularly for neuroimaging analyses, was relatively small, which may limit generalizability. Additionally, while correlations between immunological markers and neurological outcomes were statistically significant, the complex interplay between systemic inflammation, treatment effects, and individual patient factors may introduce unmeasured confounding. Finally, the study did not explore potential genetic or molecular factors that may predispose certain patients to autoimmune activation, which could be addressed in future research.

Future Directions

Future studies should consider longitudinal designs to monitor the temporal evolution of immune dysregulation and neurological function in HL. Interventional studies targeting specific cytokine pathways or T-cell populations may elucidate causal mechanisms and inform therapeutic strategies. Expanding neuroimaging analyses to include functional MRI and positron emission tomography could provide insights into regional brain activity and metabolic changes associated with immune-mediated injury. Additionally, integrating genomic and transcriptomic analyses may help identify patient-specific susceptibility factors for autoimmune activation and neurological complications.

Conclusion

This study provides evidence that autoimmune activation plays a critical role in the neurological manifestations observed in patients with Hodgkin's lymphoma (HL). HL patients exhibited systemic immune dysregulation characterized by elevated pro-inflammatory cytokines, imbalances in T-cell subsets, and the presence of autoreactive antibodies, particularly anti-neuronal antibodies. These immunological alterations were significantly associated with cognitive deficits, subtle sensory and motor impairments, and structural brain changes detected by neuroimaging, indicating that CNS dysfunction in HL can occur independently of direct tumor infiltration.

Our findings suggest a mechanistic link in which cytokine-mediated neuroinflammation, antibody-mediated neuronal effects, and T-cell-related immune activity collectively contribute to neurological compromise. The correlations observed between immune markers and cognitive performance underscore the potential of these biomarkers for early identification of patients at risk for neurological complications. Clinically, these results highlight the importance of integrating neurological assessment into HL management and considering immunomodulatory strategies to mitigate CNS effects without compromising oncologic treatment.

Overall, this study emphasizes the intersection of immunology and neurology in Hodgkin's lymphoma, providing a framework for future research on targeted interventions aimed at reducing neuroimmune-mediated morbidity and improving patient quality of life.

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