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Growing Up After Chemo: A Review of Cognitive, Behavioral, and Psychosocial Outcomes in Pediatric Cancer Survivor

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Abstract:

Background. Advances in pediatric oncology have increased survival rates above 80% in high-income countries, shifting attention toward long-term complications such as chemotherapy-induced cognitive impairment (CICI), commonly referred to as "chemobrain." This condition may persist beyond treatment and significantly affect cognitive, behavioral, and psychosocial functioning in childhood cancer survivors.

Aim. This review summarizes current knowledge on CICI in pediatric cancer survivors, which is a common late effect associated with cognitive, academic, and psychosocial difficulties that can reduce quality of life.

Material and methods. This systematic review adhered to PRISMA guidelines, searching PubMed for English-language literature (January 2015 - March 2026) regarding chemotherapy-induced cognitive impairment (CICI) in pediatric oncology populations. Search strings integrated keywords including "chemobrain," "CRCI," and "pediatric." Studies were excluded if they focused on adult cohorts, lacked cognitive assessments, or were published in languages other than English. Extracted data encompassed patient demographics, treatment protocols, and cognitive outcomes.

Results. Pediatric CICI prevalence is estimated at 40-60%, involving neuroinflammation, white matter compromise, and accelerated brain aging. Resulting deficits in memory and executive function lead to significant academic and social impairment. Diagnosis requires a multimodal framework integrating neuropsychological evaluations, neuroimaging, and biological markers.

Conclusions. CICI is a significant yet underrecognized late effect of pediatric cancer that broadly impacts cognitive, emotional, and academic development. Mitigating these effects requires early multidisciplinary management alongside research into standardized diagnostic tools and targeted interventions.

Keywords: Chemobrain, Cancer-related cognitive impairment, CICI, Pediatric

Content:

1. Introduction

Approximately 400,000 children are diagnosed with cancer worldwide each year, with survival rates in high-income countries now exceeding 80% due to advances in multimodal treatment. As survival improves, attention has shifted toward long-term treatment-related complications, including chemotherapy-induced cognitive impairment (CICI), or “chemobrain,” which can persist after treatment and affect academic, social, and functional outcomes [1,2]. Despite growing research, no comprehensive synthesis of cognitive, behavioral, and psychosocial outcomes in pediatric populations exists. This review aims to summarize current evidence on CICI in the pediatric population, focusing on clinical manifestations, assessment, and management, and to identify gaps for future research and intervention.

2. Methodology

This review was conducted in accordance with PRISMA guidelines. Literature on chemotherapy-induced cognitive impairment (CICI, “chemobrain”) in pediatric cancer survivors and pediatric oncology patients published from 01.01.2015 to 15.03.2026 was searched in PubMed. Earlier studies (n = 4) published before 2015 were included due to their high relevance to the topic, with priority given to more recent publications from the last five years. Searches used the keywords: “chemobrain” OR “cancer-related cognitive impairment” OR “CICI” OR “CRCI” AND “children” OR “pediatric” OR “adolescent” AND “chemotherapy”. Titles, abstracts, and full texts were screened, and studies were excluded if they involved only adult populations, reported solely physiological outcomes without cognitive assessment, or were non-English publications. Data were extracted on patient characteristics, treatments, assessment tools, outcomes, and interventions.The study selection process is summarized in the PRISMA flow chart (Figure 1).

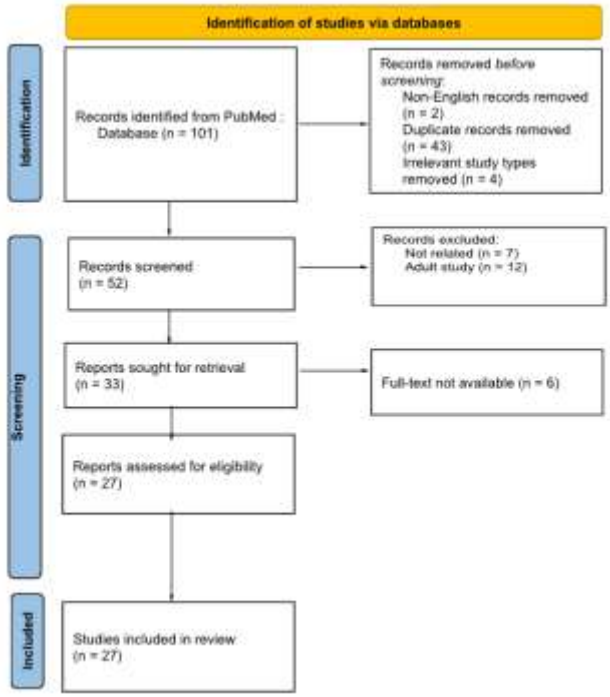

Figure 1: PRISMA flow chart

3. Chemobrain in Pediatric Cancer Survivors: Definition and Prevalence

CICI refers to a constellation of deficits affecting attention, memory, processing speed, executive function, and language abilities. In pediatric populations, the reported prevalence ranges from 40% to 60% among children treated with chemotherapy [3]. Identified risk factors include younger age at diagnosis, female sex, exposure to cranial radiotherapy, intrathecal chemotherapy (particularly methotrexate), genetic susceptibility, and lower socioeconomic status [4,5].

4. Pathophysiology

The mechanisms underlying CICI are multifactorial and not yet fully understood; however, several processes have been relatively well characterized. Proposed pathways include neuroinflammation, oxidative stress, disruption of the blood-brain barrier, and impaired neurogenesis. Chemotherapy has been associated with white matter damage, which primarily involves decreased white matter integrity due to demyelination, axonal injury, and reduced oligodendrocyte function, rather than only a global loss of brain mass. These microstructural alterations can be detected using advanced neuroimaging techniques (e.g., diffusion tensor imaging) and are particularly evident in frontal and medial brain regions [6,7].

In parallel, reduced connectivity refers to disrupted communication between brain regions, especially within frontal-subcortical networks responsible for executive functions, attention, and working memory. This disruption is thought to result from both structural damage to white matter tracts and functional alterations in neural network activity, leading to less efficient information processing [8,9]. Additionally, emerging evidence suggests that cancer treatment may induce features of accelerated brain aging, including cortical thinning and changes in subcortical structures. Abnormal protein accumulation, such as tau dysregulation, has also been observed; however, the exact mechanisms underlying tau alterations remain unclear. It is hypothesized that chronic neuroinflammation, oxidative stress, and treatment-induced neuronal injury may promote tau hyperphosphorylation and impaired clearance. These changes resemble processes observed in neurodegenerative disorders and may contribute to long-term cognitive decline [10,11].

5. Clinical Manifestations

5.1. Cognitive Outcomes

Neurocognitive impairments may arise not only as a consequence of chemotherapy, which is the primary focus of this study, but also due to other factors, including radiation therapy, surgical interventions, stem cell transplantation, and the direct effects of certain cancers; therefore, these additional contributors should be taken into account when interpreting cognitive outcomes. Neurocognitive impairments are well recognized in survivors of pediatric central nervous system (CNS) tumors and hematologic malignancies, while research in pediatric solid tumor survivors remains limited, highlighting the need to explore factors beyond treatment effects [12,13]. Childhood cancer survivors are at elevated risk of CICI, including deficits in memory, attention, processing speed, and executive function. Studies report new-onset memory impairment in up to 35% of CNS tumor survivors, 26% of acute lymphoblastic leukemia (ALL) survivors treated with cranial radiation, 14% of ALL survivors treated with chemotherapy alone, and 17% of Hodgkin lymphoma (HL) survivors, compared with under 8% of siblings [14]. Survivors of extracranial solid tumors and lymphomas also exhibit measurable cognitive deficits, with 12-18% showing global impairments and up to 50% affected in specific domains, even without CNS involvement. Risk is higher following cranial radiation, high-dose chemotherapy, and in the presence of neurological comorbidities, while lifestyle factors such as reduced screen time and higher physical activity are associated with better outcomes. These findings underscore the need for routine neurocognitive monitoring and early interventions across pediatric cancer survivor populations [12,15,16].

5.2. Behavioral and emotional outcomes

The behavioral manifestations of CICI in pediatric populations are primarily characterized by persistent deficits in memory, attention, and executive functioning. Studies report that survivors frequently describe a subjective sensation of being "mentally slow," which correlates with objective declines in information processing speed and the ability to comprehend complex instructions [9,11]. Within the academic environment, these cognitive impairments translate into significant struggles with task efficiency, organization, and the completion of assignments, often necessitating extended time and individualized support [11,14,17,18]. It has been observed that long-term survivors of childhood ALL may exhibit symptoms that mirror Attention Deficit Hyperactivity Disorder (ADHD), particularly regarding behavioral inhibition and sustained focus [19]. Sociologically, these children often find themselves in an environment where they lack social connections. Survivors of non-CNS cancers are three to four times more likely to display social skill deficits than their healthy siblings [15]. Such interpersonal challenges frequently lead to social withdrawal or, in severe cases without intervention, the development of clinical social phobia [9,17]. Emotional regulation is further compromised by the survivor's acute awareness of their reduced abilities compared to peers, which triggers significant mental distress and low self-esteem. Furthermore, research indicates a nearly 2.5 times increased risk for new-onset emotional regulation impairment in adulthood for those treated with chemotherapy-only protocols, including survivors of childhood ALL [20].

5.3. Psychological functioning and quality of life

CICI exerts a profound and lasting impact on the long-term quality of life (QOL) of childhood cancer survivors [15,21].
Biologically, chemotherapy has been associated with accelerated brain aging, manifesting in structural changes and protein aggregations- such as abnormal Tau protein - and reductions in synaptic proteins like postsynaptic density protein-95 (PSD-95), which together represent significant structural alterations paralleling neurodegenerative conditions like Alzheimer’s disease [11,18]. Biological aging process results in a slower developmental trajectory where survivors may lag behind age-expected milestones for decades [17,22]. The psychological landscape is characterized by a discrepancy between perceived and objective QOL. Survivors may report a generally good life quality while simultaneously reaching clinical levels of distress, anxiety, or depression. This psychological burden is intimately linked to a failure to meet traditional adult social milestones, including independent living, financial self-sufficiency, and stable career trajectories. Furthermore, the presence of comorbidities- specifically chronic fatigue, insomnia, and persistent pain- substantially

impairs cognitive-related QOL. This synergistic symptomatic burden poses a significant risk to the maintenance of long-term psychological well-being [15,17,21].

6. Assessment and Monitoring in Clinical Practice

6.1. Cognitive disorders

The Children's Oncology Group (COG) recommends that all pediatric oncology patients undergo neuropsychological testing, regardless of whether there are apparent signs of CNS impairment [8]. In clinical practice, a multimodal approach to the assessment and monitoring of CICI in pediatric oncology patients is recommended, integrating neuropsychological testing, behavioral rating scales, neuroimaging, and biomarker analysis to capture both objective and subjective aspects of cognitive function. Standardized neuropsychological instruments, such as the Wechsler Intelligence Scales (WPPSI for preschool children, WISC for school-aged children, and WAIS for older adolescents), remain the cornerstone for objectively assessing global cognitive abilities, including verbal comprehension, working memory, processing speed, and perceptual reasoning, enabling quantification of Full-Scale Intelligence Quotient (FSIQ) and domain-specific deficits [23]. In a systematic review and meta-analysis by Semendric et al. (2025) on cancer-related cognitive impairment (CRCI) in pediatric non-CNS cancer patients, approximately 15% of children scored below the normative range on the FSIQ (FSIQ; ≥1 SD below the population mean), indicating a significant reduction in overall cognitive functioning [15]. These tests can identify subtle impairments in executive functions and working memory that may not be apparent through global IQ measures alone and should be administered longitudinally to detect changes over time. Complementing objective tests, behavioral rating scales completed by patients, parents, or teachers provide insight into real-world executive function and behavior, particularly valuable in younger children unable to complete formal testing.

Wechsler tests (WISC, WPPSI, WAIS) have been shown to correspond with structural and functional changes observed in MRI among children treated with chemotherapy. Cognitive declines observed in pediatric oncology patients undergoing chemotherapy - particularly reductions in full-scale IQ, working memory, and processing speed - have been linked to decreased white matter integrity in frontal and medial brain regions, as evidenced by structural MRI studies. These findings underscore the utility of combining objective neuropsychological assessments with neuroimaging to comprehensively evaluate CICI [24].

Given limitations in traditional assessment tools, specialized screening batteries such as DIVERGT, which evaluates working memory, visual-motor integration, attention, and fluency, have been explored for early identification of at-risk children. Advances in computerized cognitive assessments offer promising avenues for repeated, time-efficient monitoring, though current evidence regarding

their sensitivity in pediatric oncology populations remains limited [6,25]. Neuroimaging modalities, including structural magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) and functional MRI (fMRI), provide objective correlates of brain alterations associated with cognitive deficits following chemotherapy, such as changes in white matter integrity and regional activation patterns. Structural MRI abnormalities have been reported in approximately 30-60% of pediatric patients undergoing chemotherapy, depending on the cohort and imaging methodology [26]. The most common findings include reduced white matter volume and decreased fractional anisotropy, reflecting impaired white matter integrity, particularly within frontal and subcortical regions. DTI studies have further demonstrated disrupted connectivity in up to 50% of patients, especially along frontal pathways critical for executive function [27-30]. Functional MRI and positron emission tomography (PET/CT) complement these structural assessments by providing insight into regional brain activation patterns and metabolic changes, respectively. Additionally, cerebrospinal fluid biomarkers, including tau protein, neuron-specific enolase, and markers of oxidative stress, may serve as biological indicators of neurotoxicity. Together, these multimodal approaches enhance the sensitivity of detection, inform prognosis, and support individualized monitoring strategies in pediatric patients exposed to neurotoxic chemotherapeutic regimens [31].

6.2. Behavioral and Functional Assessment

Monitoring must prioritize functional indicators, particularly academic progress including yearly screenings for absenteeism and the ability to catch up on missed work, as school performance serves as a vital indicator of cognitive status. Evaluations should move beyond "Global IQ" to target domains highly sensitive to neurotoxicity, including executive function and visual-motor integration [11,17,20].

Furthermore, clinicians must assess modifiable lifestyle factors- such as physical activity and tobacco use - which significantly influence the long-term trajectory of memory impairment.

6.3. Emotional and Regulatory Screening

Regular screening for psychological distress and emotional regulation is critical, as these symptoms are often more strongly associated with a patient’s cognitive complaints than objective test scores [18].

Complementing objective tests, the Behavior Rating Inventory of Executive Function (BRIEF) - the most commonly used tool for assessing behavioral and emotional regulation from the perspectives of patients, parents, and teachers - provides valuable insight into real-world executive functioning and behavior, particularly in younger children who are unable to complete formal testing [11]. Difficulties

reported in BRIEF domains, such as planning, organization, and inhibitory control, have been associated with altered connectivity in the frontal lobes and cingulate gyrus, reflecting everyday executive function deficits [8].

Clinical practice should include routine surveillance for anxiety, depression, and post-traumatic stress symptoms (PTSS), with a specific focus on identifying social phobia during critical transition periods like school re-entry [9].
Survivors also require vigilant monitoring for low self-esteem and suicidal ideation during long-term follow-ups [22].

6.4. Advanced Psychological and Diagnostic Monitoring

Advanced diagnostics now incorporate neuroimaging and biological markers to supplement traditional psychological tests and bridge the gap between patient-reported complaints and objective results [18].
Emerging technologies, including Machine Learning and Explainable AI (XAI) tools like SHAP, assist clinicians in attributing cognitive decline to specific brain networks, thereby increasing diagnostic trust. Furthermore, the analysis of cerebrospinal fluid (CSF) or plasma for biomarker panels- including cytokines like IL-1B, IL-6, and TNF-a - can identify inflammatory signatures that correlate with cognitive performance for up to a decade after treatment [11,18]. Computerized platforms like CogState are also being explored to provide faster, more standardized assessments of academic and cognitive abilities [11].

6.5. Psychosocial and Subjective Evaluation

Holistic assessments should emphasize the survivor's lived experience by employing qualitative methodologies to elicit the child’s authentic voice, particularly through the use of semi-structured interviews and focus groups. This approach captures the self-identified burden and internal barriers that quantitative metrics often miss. Integrating multi-informant reports, such as parent and caregiver proxy reports (that can be noticed significantly earlier than by a healthcare provider), is vital for identifying social withdrawal, difficulties in school reintegration, and emotional regulation issues that a young child may not yet be able to articulate. This comprehensive view ensures that monitoring tracks not just medical resolution, but the child's ability to navigate social landscapes and achieve long-term functional independence [9,11,17].

7. Management and support strategies

Management strategies must be multi-faceted, addressing the biological, environmental, and academic needs of the survivor.
Academic support remains the cornerstone of intervention. Formal statements of special educational needs and the early implementation of Individualized Education Programs (IEPs) in schools are crucial to maintain academic progress. The introduction of such an agreement would bridge the organisational gap that currently exists between healthcare providers and educational institutions, advocating for the child's specific neurocognitive needs.
Non-pharmacological interventions, including behaviorally oriented cognitive training and regular physical activity, have demonstrated efficacy in improving both objective performance and perceived cognitive functioning.
Mind-body techniques such as mindfulness-based stress reduction (MBSR) and biofeedback also offer potential for mitigating emotional symptoms. In specialized cases, medical advancements like proton beam therapy (PBT) or targeted tyrosine kinase inhibitors (TKIs) are recommended. PBT to minimize radiation-induced damage to healthy tissues and TKIs being a promising alternative to traditional chemotherapy. Pharmacotherapy, while an option for refractory cases, remains a secondary line of treatment due to conflicting data regarding the efficacy of CNS stimulants and anti-dementia medications [9,17,21].

8. Implications for family medicine and psychological care

Primary care providers must embrace a life-long surveillance model, recognizing that neurocognitive "late effects" may not manifest until decades after the cessation of treatment. It is imperative that clinicians acknowledge the validity of cognitive decline in all survivors, including those treated with chemotherapy-only protocols who were previously thought to be at lower risk.
Furthermore, practitioners should focus on modifiable risk factors, such as the patient's age, genetics (variants APOE4, ALDH2, and COMT) and detailed treatment history (chemo-/ radiotherapy). Aggressive management of cardiovascular comorbidities, smoking cessation, and the promotion of physical activity can significantly mitigate the trajectory of late-onset memory impairment [19].
Effective care necessitates a multidisciplinary approach that coordinates between oncology, neuropsychology, and school systems to safeguard the survivor's developmental trajectory into adulthood. Family physicians should also be equipped with universal resources to help families navigate the transition from hospital to school, ensuring that survivorship frameworks remain patient-centered and responsive to the self-identified barriers reported by the survivors themselves.

9. Limitations of the study

The lack of standardized testing, the need for patient cooperation, and the time-consuming nature of assessments constitute significant challenges for physicians caring for pediatric patients. Another issue arises from the specific characteristics of the studied population, which is marked by continuous cognitive development associated with CNS maturation. This makes it difficult to compare results from sequential tests in the same patient and to interpret them accurately. A further limitation is the lack of uniformity in the study populations; some studies include pediatric oncology patients, some pediatric cancer survivors, whilst others focus on adult survivors; this too may contribute to ambiguity in the research findings.

Moreover, due to the influence of emotional factors on the evaluation of a child's functioning in subjective psychological tests, these tools cannot be used as sensitive indicators for detecting chemobrain-type disorders. Further research is therefore necessary to develop psychological tests that are both sufficiently effective in identifying impairments and, at the same time, quick to administer and easily accessible.

10. Conclusions

CICI represents a significant and often underrecognized late effect of pediatric cancer treatment. Its impact extends beyond cognitive domains, affecting emotional functioning, academic performance, and long-term independence.

Early identification, longitudinal monitoring, and multidisciplinary management are essential to mitigate these effects. Future research should focus on the development of sensitive, standardized, and clinically feasible diagnostic tools, as well as targeted interventions to improve long-term outcomes in childhood cancer survivors.

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consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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