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Research Article

Humoral Immunity to Vaccine-Preventable Diseases in Childhood Cancer Survivors: A Single-Center Study

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Abstract

Background: Pediatric cancer treatments significantly impair immune memory. This study aims to evaluate the prevalence of protective vaccine-induced antibodies and characterize immune recovery in children following chemotherapy in Algeria.

Methods: A prospective study was conducted on 75 pediatric patients (median age: 6 years) in remission after cancer treatment at Mustapha University Hospital. Humoral immunity was assessed for measles, hepatitis B (HBV), diphtheria and tetanus. Cellular immunity and immunoglobulin levels were analyzed at a median of six months post-treatment.

Results: Overall, 94.6% of patients exhibited an absence of protective antibodies against at least one vaccine-preventable disease. Seronegativity rates were highest for measles (76%) and HBV (64%), followed by diphtheria (34%) and tetanus (29%). Patients with Acute Leukemia (AL) showed significantly higher rates of tetanus seronegativity compared to those with non-Hodgkin lymphoma (45.2% vs. 6.7%, $p = 0.008$). Immunological evaluation revealed profound $CD4^+$ T-cell lymphopenia in 45% of cases. Age was significantly associated with serological status (HBV: $p = 0.01$; diphtheria: $p = 0.04$).

Conclusions: A substantial proportion of pediatric cancer survivors lose humoral immunity, particularly against measles and HBV. These findings highlight a critical window of vulnerability and strongly support the implementation of systematic post-treatment serological screening and tailored revaccination strategies.

Keywords: Pediatric Oncology; Vaccination; Humoral Immunity; Measles; Hepatitis B; Chemotherapy; Algeria

Introduction

Over the past two decades, substantial progress has been achieved in the prognosis of childhood cancers. However, survivors remain at risk of long-term treatment-related complications, including secondary immunodeficiency. Immune dysfunction may be directly related to the underlying hematologic malignancy or induced by anticancer therapies, particularly chemotherapy and radiotherapy [1-4].

Consequently, vaccine-induced antibody levels frequently diminish during and after cancer treatment, leaving these vulnerable patients susceptible to vaccine-preventable infections [5,6]. Additionally, this group may play a significant role in the dissemination of infectious agents within the community. In Algeria, the reported incidence of childhood and adolescent cancers in 2019 was approximately 59.4 per 100,000 among boys and 50.2 per 100,000 among girls [7]. Despite the importance of this population, information regarding post-treatment vaccine-induced serological protection and immune recovery remains limited among Algerian pediatric cancer survivors.

The primary aim of this study was to evaluate the post-vaccination serological status of children treated for cancer following the completion of chemotherapy and/or radiotherapy. Secondary objectives were to assess the kinetics of immune reconstitution and to identify potential risk factors associated with the absence of post-vaccination protective antibodies.

Material and Methods

Study Design and Population

A prospective study was conducted at the Pediatric Oncology Department of Mustapha University Hospital (Algiers). Children who completed oncologic treatment between July 2019 and December 31, 2021, were consecutively enrolled. Inclusion criteria were: age < 16 years, confirmed malignancy in complete remission and discontinuation of therapy for at least three months. Patients who had undergone Hematopoietic Stem Cell Transplantation (HSCT) were excluded.

Demographic and clinical data collected included age, sex, cancer diagnosis and type of oncologic treatment received. Treatment intensity was classified using the Intensity of Treatment Rating scale [8]. Vaccination status at diagnosis was verified using the patients' vaccination records.

Serological and Immunological Assays

Post-vaccination antibody levels against tetanus and diphtheria toxoids were quantified using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) (The Binding Site), with a protective threshold defined as 0.1 IU/m. Serum anti Hepatitis B surface antigen (HBs) levels were measured by Chemiluminescent Microparticle Immunoassay (CMIA) on the ARCHITECT i1000SR analyzer (Abbott Laboratories); a concentration ≥ 10 mIU/mL was considered protective.

Finally, measles-specific IgG antibodies were screened in patient sera using an Enzyme Immunoassay (EIA) (Euroimmun, Germany), with a positivity cut-off set at a ratio of 1.1. Immune reconstitution was assessed by white blood cell counts, immunonephelometry (IgG, IgA, IgM) and lymphocyte phenotyping ($CD45^+$, $CD19^+$, $CD3^+$, $CD4^+$, $CD8^+$ and NK cells) using flow cytometry [9,10]. The parameters were determined within 3 months after cessation of treatment and 12 months later.

Statistical Analysis

Data were analyzed using EpiData. Quantitative variables are expressed as mean ±SD. Proportions were compared using the Chi-square or Fisher's exact test. Logistic regression was performed to identify factors associated with the absence of seroprotection. A p-value < 0.05 was considered significant.

Ethical Considerations

Participation in this study was voluntary. Written informed consent was obtained from all parents or legal guardians prior to enrollment.

Results

Study Population Characteristics

A total of 75 eligible patients were enrolled in the study. Humoral immunity was assessed in all 75 patients, whereas cellular immunity analysis was available for 71 patients. The age of the patients ranged from 11 months to 14 years and 11 months, with a median age of 6 years. The cohort included 50 boys and 25 girls. Most patients (92%) were treated for malignant hematologic diseases, while 8% had solid tumors. Malignant hematologic diseases consisted mainly of acute leukemia (54.7%) and lymphoma (37.3%). Solid tumors included nephroblastoma (6.7%) and neuroblastoma (1.3%).

All patients received chemotherapy and 18% also underwent radiotherapy. Three patients received immunotherapy, including anti-CD20 monoclonal antibodies (n = 2) and a tyrosine kinase inhibitor (n = 1). Based on the Intensity Treatment Rating (ITR) scale, 37.3% of patients received mild to moderate treatment and 62.6% were treated with intensive to very intensive modalities.

Vaccination Status and Serological Immunity

Using the vaccination cards, 81.5% were vaccinated as per the Algerian Expanded Program on. Immunization (EPI) 2008 calendar and 18.5% according to the program implemented in 2016 [11]. 80% of children were fully vaccinated against diphtheria, tetanus (primary doses) and hepatitis B, but only about 40% for measles (2 doses). Overall, 94.6 % of patients lacked protective antibodies against at least one vaccine-preventable disease. Seronegativity rates were 76% for measles, 64% for hepatitis B, 34% for diphtheria and 29% for tetanus.

Serological Immunity According to Type of Malignancy

The absence of post-vaccination antibodies for measles, hepatitis B and diphtheria was more frequent among children treated for malignant hematologic diseases compared with those treated for solid tumors; however, these differences were not statistically significant.

When comparing patients with acute leukemia to those with non-Hodgkin lymphoma, seronegativity rates were higher in children with acute leukemia for all antigens studied. This difference reached statistical significance for tetanus, with 45.2% of children with acute leukemia lacking protective antibodies compared with 6.7% of those with non-Hodgkin lymphoma ($p = 0.008$) (Table 1).

Impact of Treatment Intensity

Lack of seroprotection for hepatitis B, diphtheria and tetanus was more frequently observed in children who received intensive or very intensive treatment protocols compared with those treated with lower-intensity regimens. However, these differences were not statistically significant.

Immune Evaluation

At study inclusion, total white blood cell counts were below the 3rd percentile for age in 8% of patients, while lymphocyte counts were below the 3rd percentile in 16% of cases. Analysis of lymphocyte subpopulations revealed that the most frequently affected cells were $CD4^+$ T lymphocytes, with values below the 3rd percentile observed in 45% of patients. This was followed by $CD3^+$ T lymphocytes (33.8%), $CD8^+$ T lymphocytes (23.8%), Natural Killer (NK) cells (25.4%) and $CD19^+$ B lymphocytes (16.9%) (Fig. 1). Regarding humoral immunity, serum immunoglobulin levels were below the age-adjusted 3rd percentile in 6.7% of patients for IgG, 8% for IgA and 16% for IgM (Fig. 2). The mean time to immune recovery was 8+/-3 months after treatment completion.

Factors Associated with Lack of Seroprotection

No significant association was observed between sex and the absence of seroprotection for measles, hepatitis B, tetanus or diphtheria ($p > 0.05$ for all antigens). Age was significantly associated with the absence of seroprotection for certain antigens. Hepatitis B seronegativity was more frequent in older children (mean age 9.07 ± 4.05 years vs. 6.65 ± 3.84 years: $p = 0.01$), whereas diphtheria seronegativity predominated in younger children (6.86 ± 3.66 years vs. 8.91 ± 4.21 years: $p = 0.04$). For measles and tetanus, seronegativity tended to be more frequent in younger children, but these differences did not reach statistical significance The absence of seroprotection was more frequent among children treated for malignant hematologic diseases compared with those treated for solid tumors; however, these differences did not reach statistical significance for any antigen. Similarly, treatment intensity was not significantly associated with seronegativity for measles, hepatitis B, tetanus or diphtheria (Table 2).

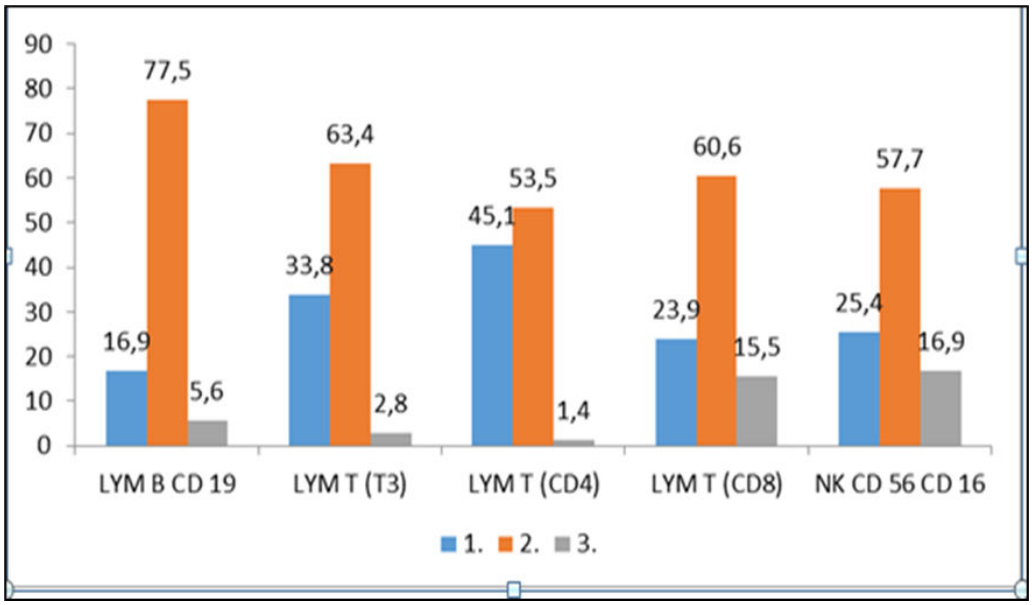

Figure 1: Lymphocyte subpopulation relative to age-adjusted percentiles (45% $CD4^+$ deficit).
1: values below the 3rd percentile; 2: values between the 3rd and 90th percentile; 3: values above the 90th percentile.

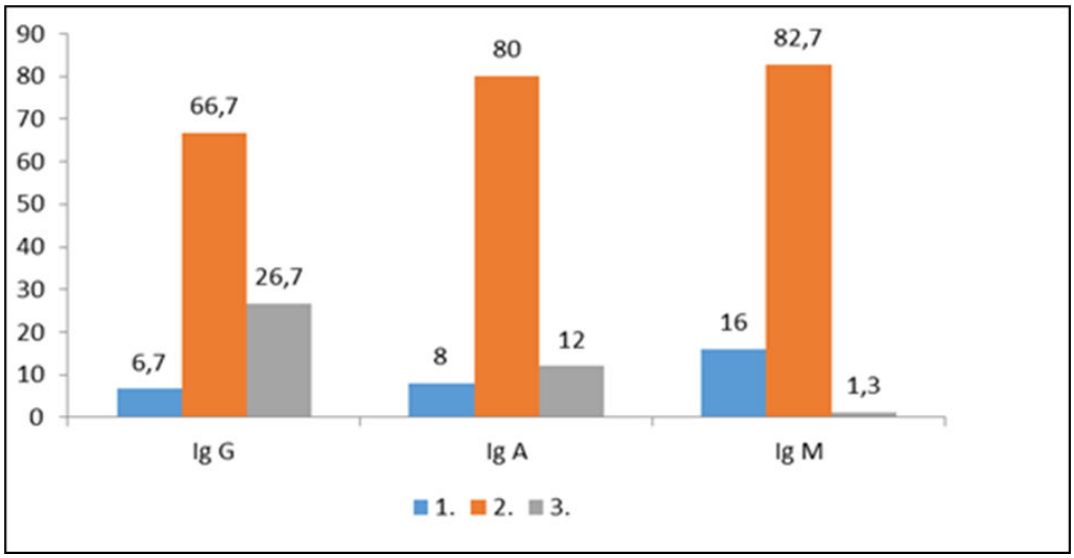

Figure 2: Serum immunoglobulin levels (IgG, IgA, IgM) relative to age-adjusted normal ranges. 1: Values below the norm for age; 2: Values within the norm for age; 3: Values above the norm for age.

Lack of Antibodies	HM vs. ST (n/N, %)	*p*-value	AL vs. NHL (n/N, %)	*p*-value
Measles	53/69 (76.8%) vs. 4/6 (66.7%)	0.44	22/31 (71.0%) vs. 12/15 (80.0%)	0.39
Hepatitis B	45/61 (73.8%) vs. 3/6 (50.0%)	0.37	23/31 (74.2%) vs. 11/15 (73.3%)	0.60
Diphtheria	25/69 (36.2%) vs. 1/6 (16.7%)	0.31	15/31 (48.4%) vs. 5/15 (33.3%)	0.26
Tetanus	20/69 (29.0%) vs. 2/6 (33.3%)	0.57	14/31 (45.2%) vs. 1/15 (6.7%)	0.008

Table 1: Serologic immunity for various vaccine antigens according to type of malignancies.

Factor	Measles	HBV	Tetanus	Diphtheria
Gender / negative serology				
M vs. F (N) (%)	38/50 vs 19/25 (76% vs 76%)	32/50 vs 16/25 (64% vs 64%)	13/50 vs 9/25 (26% vs 36%)	17/50 vs 9/25 (34% vs 36%)
p	1	1	0.37	0.86
Median Age at enrollment				
(pos. serology) vs (neg. serology)	8.74 ± 3.74 vs 8.03 ± 4.25	6.65 ± 3.84 vs 9.07 ± 4.05	8.74 ± 4.2 vs 6.91 ± 3.71	8.91 ± 4.21 vs 6.86 ± 3.66
p	0.53	0.01	0.08	0.04
Type of pathology				
HM vs. ST (neg. serology) (N) (%)	53/69 vs 4/6 (76.8% vs 66.7%)	45/61 vs 3/6 (73.8% vs 50.0%)	20/69 vs 2/6 (29.0% vs 33.3%)	25/69 vs 1/6 (36.2% vs 16.7%)
p	0.44	0.37	0.57	0.31
Treatment intensity				
Low/Mod vs. High (neg. serology)	22 (78.6%) vs 35 (74.5%)	16 (57.1%) vs 32 (68.1%)	8 (28.6%) vs 14 (29.8%)	8 (28.6%) vs 18 (38.3%)
p	0.68	0.34	0.9	0.39

Table 2: Factors Associated with the absence of seroprotection for vaccine-preventable diseases.

Discussion

Children diagnosed with cancer usually have followed vaccinations according to the age-appropriate national immunization schedule. In Algeria, vaccination coverage has progressively improved since the implementation of the national immunization program in the 1960s, leading to a substantial reduction in vaccine-preventable diseases and the elimination or eradication of several infections, such as neonatal and maternal tetanus, smallpox and poliomyelitis [12]. Children treated for cancer experience profound alterations in immune function related both to the malignancy itself and to anticancer therapies. Several studies have assessed vaccine-induced antibody levels exclusively after the completion of treatment, as was the case in our study [13-17,32]. Other studies evaluating antibody levels before and after treatment have consistently reported a loss of seroprotection, with significant variability according to vaccine type. A limited number of studies have further examined antibody kinetics following revaccination [18-20].

In the present study, an absence of protective immunity was observed in 76% of children for measles, 64% for hepatitis B, 34% for diphtheria and 29% for tetanus. These findings are consistent with previous reports. Fayea and Garonzi reported seronegativity for at least one vaccine-preventable disease in more than 90% and 83% of children, respectively [21,22]. Similarly, in our cohort, more than 94% of patients lacked protective antibodies against at least one antigen. The seroprotection rate against measles (24%) observed in our study is particularly low compared with data from the literature, where higher rates have generally been reported [14,23-25]. Previous studies have shown that the risk of measles after treatment for acute leukemia ranges from 25% to 71% reflecting a marked decline in protective antibodies compared with healthy children [1,3,26]. Aytaç, et al., reported measles seronegativity in 58% of children treated for acute leukemia, with low seroconversion rates following revaccination [27]. These results indicate that a substantial subset of survivors remains exposed to measles after chemotherapy.

Nordøy, et al., demonstrated that chemotherapy can induce a loss of immunity conferred by prior Measles-Mumps-Rubella (MMR) vaccination [28]. Feldman, et al., similarly observed post-chemotherapy seronegativity in pediatric oncology patients previously vaccinated against measles, with seropositivity rates significantly lower than those expected in the general population [29]. Regarding hepatitis B, several studies have shown a decline in vaccine-induced immunity following chemotherapy for Acute Lymphoblastic Leukemia (ALL). In our study, 64% of patients lacked protective anti-HBs antibodies, corresponding to a seroprotection rate of 36%, which is comparable to results reported by Brodtman, et al. Existing literature describes seroprotection rates ranging between 29.6% and 57.4% [21,22,31]. Kazem Ghaffari, et al., demonstrated a significant decrease in Ac anti-HBV levels six months after completion of treatment, while Shin et al. reported a dramatic decline in protective antibodies after chemotherapy, further supporting the negative impact of treatment on hepatitis B immunity [20,30].

The absence of post-vaccination antibodies against measles, hepatitis B and diphtheria was more common among children treated for malignant hematological disorders in our cohort than among those with solid tumors. Furthermore, the incidence of seronegativity for diphtheria was significantly higher among children treated for acute leukemia than those treated for lymphoma. These results are supported by Bochennek, et al., who described a greater loss of vaccine-induced immunity in children treated for ALL compared to those with other malignancies [14]. Immunological evaluation in our study revealed reduced B-cell counts and decreased IgM and IgA levels, while IgG levels were relatively preserved. Natural killer cells were minimally affected, whereas prolonged $CD4^+$ T-cell lymphopenia was frequently observed. These patterns are consistent with previously published data and reflect the differential impact of chemotherapy on specific immune cell subsets [33].

Overall, our findings highlight a high prevalence of inadequate post-vaccination seroprotection in children in remission after cancer treatment, particularly against measles and hepatitis B. This population remains at increased risk for severe infections and may contribute to the transmission of vaccine-preventable diseases.

The main limitation of our study is the absence of baseline serological data at the time of cancer diagnosis, which would have allowed direct confirmation of treatment-induced loss of immunity. Additionally, the lack of a healthy control group limits comparison with the general pediatric population. These constraints were primarily related to logistical and financial limitations.

Conclusion

In conclusion, our data demonstrate that a substantial proportion of pediatric cancer survivors lose humoral immunity against measles and hepatitis B after the completion of chemotherapy. These results strongly support systematic post-treatment serological assessment and the revaccination of seronegative children. Future prospective studies are needed to determine whether revaccination induces durable protective immunity and to define optimal revaccination schedules. Implementing well-designed revaccination strategies is essential to ensure adequate long-term protection in this vulnerable population.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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None.

Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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