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REVIEW ARTICLE

Endocrine sequelae in childhood cancer survivors☆

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Abstract Thanks to the advances in cancer treatment, the five-year survival rate after childhood cancer has increased up to 80%. Therefore 1/500 young adults will be a survivor. Endocrine sequelae are most common, affecting 40–60% of survivors. The most frequent sequelae include growth failure and gonadal and thyroid diseases. Sequelae occur more frequently in survivors from central nervous system tumors, leukemia, and lymphoma. Their development will depend on the type of cancer, its location, age at diagnosis, and treatment administered. Treatments associated to more endocrine sequels are cranial radiotherapy and hematopoietic cell transplantation. Because of the high prevalence of endocrine sequelae, international guidelines recommend endocrinologists to prospectively evaluate the survivors. As some of these endocrine changes will not develop until adult life, transition programs should be implemented, and active investigation should be made to decrease the endocrine consequences of cancer treatment.

PALABRAS CLAVE
Secuelas endocrinas;
Superviviente cáncer infantil;
Hipopituitarismo;
Disfunción gonadal

Secuelas endocrinológicas en supervivientes de cáncer infantil

Resumen La evolución en los tratamientos oncológicos ha supuesto un aumento de la supervivencia del cáncer infantil cercana al 80% a 5 años, por lo que 1/500 adultos jóvenes será un superviviente. Las secuelas endocrinas son las más comunes y afectan al 40–60%, siendo las más frecuentes las alteraciones del crecimiento y la disfunción gonadal y tiroidea. Los pacientes con tumores del sistema nervioso central, leucemias y linfomas son los que presentan más secuelas, y estas dependen del tipo de cáncer, su localización, la edad de diagnóstico y el protocolo de tratamiento; las terapias de mayor riesgo son la radioterapia craneal y el trasplante de

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progenitores hematopoyéticos. Dado este elevado riesgo, las guías internacionales recomiendan a los endocrinólogos evaluar prospectivamente a los supervivientes. Algunas de las alteraciones endocrinas no se manifestarán hasta la vida adulta, por lo que debemos crear programas de transición, así como ser activos en la investigación para reducir las secuelas endocrinas de los tratamientos del cáncer.

Introduction

The evolution of cancer treatments has resulted in improvements in the 5-year survival rate, reaching 80% for all cancers globally, and 90% in the case of leukemias and lymphomas. Approximately one out of every 285 children is diagnosed with cancer, and one out of every 530 young adults is a cancer survivor.[1] According to the Spanish Pediatric Tumor Registry (*Registro Español de Tumores Pediátricos*),[2] a total of 25,100 cases of malignant disease were recorded in patients between 0 and 14 years of age in the period between 1980 and 2015. This gives us an idea of the number of young adults in this country that survive childhood cancer. It has also been reported that 62% of all adult survivors experience some medical sequelae, and that 40–60% suffer endocrine disease. This implies a risk far greater than that found in the general population.[3,4]

The present review offers a global view of the follow-up of pediatric cancer survivors, focusing on current knowledge regarding endocrine sequelae, with the aim of optimizing follow-up and improving long-term survival.

New cancer treatment perspectives in children and adolescents

The most common cancers in the pediatric population are leukemias, lymphomas and tumors of the central nervous system (CNS) (Table 1). The sequelae among the survivors depend on the type of cancer, its location, patient age at the time of diagnosis, and the treatment protocol used (radiotherapy fractionation and dose; type and cumulative dose of chemotherapy). The changes in leukemia management include the identification of risk factors, the intensification of treatment and improvements in supportive measures, a lesser use of prophylactic radiotherapy, and the introduction of hematopoietic progenitor cell transplantation (HPCT) in cases of relapse, all of which have contributed to improve patient survival. In some diseases such as Hodgkin's lymphoma or Wilms tumor, where the survival rates are high, the current aim is to reduce their sequelae. Other diseases such as malignant astrocytomas or metastatic sarcomas continue to have a poor prognosis, and the aim in such cases is to develop new therapies capable of improving survival.[5,6]

Long-term sequelae in childhood cancer survivors

The review conducted by the Childhood Oncology Group (COG) revealed shortcomings in survivor control: 68% of the patients treated between 1970 and 1986 had not undergone regular controls, and 39% had had no contact with the center that had treated them.[3] The different cohorts studied to date involve different methodological approaches, though they report a comparable risk of medical problems.[7] In order to adequately estimate excess risk, some cohorts such as the Childhood Cancer Survivor Study or the Adult Life after Childhood Cancer in Scandinavia survey have compared the incidence with a cohort of siblings of the survivors or with a comparable healthy population.[4,8] As a result of these studies, in 2003 the COG published a clinical guide (COG-LTFU Guidelines) with concrete recommendations regarding the follow-up of survivors, and with a specific section addressing endocrine sequelae.[9]

In this regard, endocrine problems are among the most frequently described sequelae, along with cardiovascular disease. Survivors of tumors of the CNS, leukemias and Hodgkin's lymphoma are the patients that experience most sequelae. The Adult Life after Childhood Cancer in Scandinavia cohort presented a relative risk (RR) for endocrine disease of 4.8 (95%CI 4.6–5.0), with higher values among those under 20 years of age. The Childhood Cancer Survivor Study in turn described the relative risks regarding hypothyroidism (RR 14.3; 95%CI 9.7–21.0), growth hormone (GH) deficiency (RR = 277.8; 95%CI 111.1–694.9), the need for the induction of puberty (RR = 86.1; 95%CI 31.1–238.2) and osteoporosis (RR = 24.7; 95%CI 9.9–61.4). Endocrine disorders moreover have implications in terms of long-term cardiometabolic morbidity in the adult, which affects 18% of all survivors.[3,4] Few studies have described the prevalence of endocrine disease with prospective application of the COG-LTFU guidelines. One of the largest series describes 519 patients with non-CNS tumors evaluated an average of 7.2 years after diagnosis, with a mean patient age of 12.1 years. Endocrine sequelae were present in 57.6% of the cases.[10] Following the introduction of the cancer survivor follow-up unit at our center, we reviewed the endocrine sequelae of 194 patients (including tumors of the CNS) with a mean age of 10 years, 5.2 years after treatment. Sixty-three percent of the patients had some endocrine disorder. Furthermore, on their first visit almost 30% of the survivors