Cancer Treatment Reviews 35 (2009) 616–632

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

COMPLICATIONS OF TREATMENT

Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: A systematic review

Renée L. Mulder [a,*], Leontien C.M. Kremer [a], Hanneke M. van Santen [b], Jan Lucas Ket [c], A.S. Paul van Trotsenburg [b], Caro C.E. Koning [d], Antoinette Y.N. Schouten-van Meeteren [a], Huib N. Caron [a], Sebastian J.C.M.M. Neggers [e], Elvira C. van Dalen [a]

[a] Department of Paediatric Oncology, Emma Children's Hospital/Academic Medical Center, F8 Noord, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
[b] Department of Paediatric Endocrinology, Emma Children's Hospital/Academic Medical Center, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands
[c] Department of Paediatrics, Waterlandziekenhuis, P.O. Box 250, 1440 AG Purmerend, The Netherlands
[d] Department of Radiation Oncology, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
[e] Department of Paediatric Oncology/Haematology, Erasmus University Medical Center/Sophia Children's Hospital & Department of Medicine, Section Endocrinology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 27 February 2009
Received in revised form 11 June 2009
Accepted 15 June 2009

Keywords:
Growth hormone deficiency
Childhood cancer survivors
Cranial radiotherapy
Systematic review

SUMMARY

Background: Growth hormone deficiency (GHD) is usually the first and most frequent endocrine problem occurring after cranial radiotherapy (CRT). The aim of this systematic review was to evaluate the existing evidence of the prevalence and risk factors of radiation-induced GHD in childhood cancer survivors.
Methods: MEDLINE, EMBASE and CENTRAL were searched for studies reporting on radiation-induced GHD in childhood cancer survivors. Information about study characteristics, prevalence and risk factors was abstracted and the quality of each study was assessed. A meta-regression analysis was performed.
Results: The prevalence of radiation-induced GHD was estimated in 33 studies. Most studies had methodological limitations. The prevalence varied considerably between 0% and 90.9%. Selecting only the studies with adequate peak GH cut-off limits (<5 μg/L) resulted in 3 studies. In these studies the prevalence ranged from 29.0% to 39.1%, with a pooled prevalence of 35.6%. Higher CRT dose and longer follow-up time have been suggested to be the main risk factors of GHD by studies included in this review. The meta-regression analysis showed that the wide variation in the prevalence of GHD could be explained by differences in maximal CRT dose.
Conclusions: GHD is a frequent consequence after CRT in childhood cancer survivors. The prevalence of radiation-induced GHD ranged from 29.0% to 39.1% when selecting only studies with adequate peak GH cut-off limits. Higher CRT dose and longer follow-up time are the main risk factors. More well-designed studies are needed to accurately estimate the prevalence of GHD and to define the exact CRT threshold dose.

Introduction

As a result of more effective treatments for childhood cancer, survival rates have greatly improved. Today, most children diagnosed with cancer are expected to become long-term cancer survivors.[1] The 8-year disease-free survival reaches now nearly 70–80%.[2] Unfortunately, the improved prognosis has resulted in the occurrence of late, treatment-related complications. In a cohort of 1.362 childhood cancer survivors, nearly 75% experienced one or more long-term effects, frequently involving the endocrine system.[3]

Survivors of childhood cancer who received cranial radiotherapy (CRT) (either the whole brain or a part of the brain) or total body irradiation (TBI) in preparation for bone marrow transplantation (BMT) are at risk of developing a deficiency of one or more hormones produced by the hypothalamus and pituitary gland (HP region). Growth hormone deficiency (GHD) is usually the first and most frequent endocrine problem occurring after radiation of the HP region.[4–6] In addition, childhood cancer survivors who underwent surgery to the brain, especially to the region where the hypothalamus and pituitary gland are located, have an increased risk of developing GHD as well.[7,8]

Radiation-induced GHD that develops in childhood may affect linear growth. When GHD persists after the completion of growth,

* Corresponding author. Tel.: +31 20 5666370; fax: +31 20 6912231.
E-mail addresses: r.l.mulder@amc.uva.nl (R.L. Mulder), l.c.kremer@amc.uva.nl (L.C.M. Kremer), h.m.vansanten@amc.uva.nl (H.M. van Santen), jlket@wlz.nl (J.L. Ket), a.s.vantrotsenburg@amc.uva.nl (A.S. Paul van Trotsenburg), c.c.koning@amc.uva.nl (C.C.E. Koning), a.y.n.schouten@amc.uva.nl (A.Y.N. Schouten-van Meeteren), h.n.caron@amc.uva.nl (H.N. Caron), s.neggers@erasmusmc.nl (S.J.C.M.M. Neggers), e.c.vandalen@amc.uva.nl (E.C. van Dalen).

0305-7372/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ctrv.2009.06.004

consequences include reduced lean body mass and bone mineral density, increased fat mass with a preponderance of abdominal adiposity, an adverse lipid profile, and increased cardiovascular morbidity. Moreover, muscle strength and exercise performance may be reduced. Impaired quality of life and psychological complaints are also common.[9,10] It has been suggested that risk factors like higher CRT dose, larger fraction size or larger number of fractions, increased volume of the HP region exposed, higher biological effective dose (BED), younger age at treatment and longer follow-up time affect the risk of GHD secondary to radiation of the HP region. In addition, gender may also influence the prevalence of GHD.[6,11] GHD can be defined either auxologically (growth) or biochemically (different diagnostic tests).[5,10]

For the development of future treatment policies, and to reduce the occurrence of endocrine late effects in childhood cancer survivors, more insight into the prevalence and risk factors of radiation-induced GHD is essential. In this way adequate follow-up protocols can be established to reduce the consequences of GHD. In this systematic review an evaluation is made of all available evidence of the prevalence and risk factors of radiation-induced GHD in childhood cancer survivors.

Methods

Search strategy for identification of studies

The objective of the literature search was to identify all studies reporting on the prevalence and risk factors of radiation-induced GHD in childhood cancer survivors. The selection process involved four steps.

First, MEDLINE/PubMed (from 1966 to March 1, 2008), EMBASE/Ovid (from 1980 to March 1, 2008), and The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, issue 1 2008) were searched for potentially relevant articles. The sensitive search strategy used for MEDLINE/PubMed is presented in Table 1. For EMBASE and CENTRAL we used adaptations of this search strategy.

Second, articles which possibly met the following inclusion criteria were selected on the basis of title and abstract by two reviewers (RM, EvD/JLK/PvT/HvS) and retrieved for more detailed examination: (1) original report (all study designs with the exception of case reports), (2) published in English (3) study population of at least 20 childhood cancer survivors (irrespective of the duration of survival time) treated with radiotherapy involving the brain, (4) prevalence of GHD as outcome (GHD defined by the authors of the original studies; studies in which GHD was defined solely as growth deviation were excluded), and (5) less than 5% of the study population diagnosed with craniopharyngioma, hypothalamic/chiasmatic glioma, or optic (nerve) glioma. These tumours are lesions of the HP region. These tumours are very likely to cause GHD, either by acting directly on HP function or indirectly by disturbing the normal connections between the hypothalamus and the pituitary gland.

Third, all articles selected in the second step were obtained in full and screened by two reviewers (RM, JLK/HvS) to ensure that they met the inclusion criteria. Finally, the bibliographies of all included studies and reviews were searched for additional references (RM, EvD). Inter-observer agreement was calculated for the second and third step of the selection process. In case of disagreement, the abstracts and articles were re-examined and discussed until consensus was achieved. If disagreement persisted a third author (LK or EvD) was consulted.

Data extraction

From each included study, the following information was abstracted by one reviewer (RM): study design, original cohort, described study group, study group of interest, study group with GH testing, control group (if applicable), cancer treatment, follow-up, and prevalence and risk factors of radiation-induced GHD. Data-extraction was checked by another reviewer (JLK/PvT/HvS/SN). In case of doubt a third author (LK or EvD) was consulted.

The patients of the original cohort represent the whole original group of childhood cancer survivors. The patients of the described study group are the childhood cancer survivors included in the study. The patients of the study group of interest are the childhood cancer survivors who have been treated with CRT. Finally, the patients of the study group with GH testing are the childhood cancer survivors who have been tested for GHD as well.

When descriptive characteristics and outcomes of children treated with CRT were lacking, data of the described study group were used and this was stated.

Quality assessment of the included studies

The quality assessment criteria are described in Table 2. The quality assessment was based on previous checklists for observational studies according to Evidence-Based Medicine Criteria.[12,13] Two reviewers (RM, JLK/HvS/PvT/SN) assessed the external and internal validity of the included studies, concerning the formation of the study group, the follow-up and outcome assessments, and the methods used for risk estimation (if applicable) in each study. In case of doubt a third author (LK or EvD) was consulted.

Table 1
Search strategy for MEDLINE/PubMed.

1.	survivor OR survivors OR long-term survivors OR long term survivors OR long-term survivor OR survivor, long-term OR survivors, long-term OR survivo*
2.	leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR leukemia lymphocytic acute OR leukemia, lymphocytic, acute[mh]
3.	growth hormone OR growth hormone, pituitary OR pituitary growth hormone OR somatotropin OR growth hormon* OR somatotropi* OR GH OR human growth hormone OR growth hormone, human OR hGH OR somatropin OR somatropi* OR insulin-like growth factor I OR insulin-like growth factor 1 OR IGF-1 OR IGF-I OR insulin like growth factor I OR insulin like growth factor 1 OR somatomedin C OR insulin-like somatomedin peptide I OR insulin like somatomedin peptide I OR insulin-like somatomedin peptide 1 OR insulin like somatomedin peptide 1 OR insulin-like growth factor binding protein 3 OR insulin like growth factor binding protein 3 OR IGF-binding protein 3 OR IGF binding protein 3 OR IGFBP-3 OR growth hormone deficiency OR growth hormone deficien* OR GHD OR GH deficiency OR GH deficien* OR growth disorder OR growth impairment OR growth deviation OR insulin tolerance test OR growth hormone provocative test OR GH provocative test OR arginine stimulation test OR ITT
4.	1 AND 2 AND 3