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Adrenal function in adult long-term survivors of nephroblastoma and neuroblastoma

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Abstract ***Background:*** Adrenal insufficiency, or relative insufficiency, might partly explain increased mortality rates in nephroblastoma and neuroblastoma survivors after unilateral adrenalectomy.

Objective: To assess adrenal function and its metabolic effects in survivors after adrenalectomy.

Methods: In this cross-sectional study, 67 adult long-term survivors of nephroblastoma, 36 survivors of neuroblastoma and 49 control subjects participated. Adrenal function was assessed by a 1 μg short Synacthen-test. Levels of cortisol, adrenocorticotrophic hormone (ACTH), low (LDL-C) and high-density lipoprotein-cholesterol (HDL-C), triglycerides, apolipoprotein-B, glucose and insulin were assessed in blood samples taken at baseline. In addition, cortisol levels were assessed after 30 ($t = 30$) and 60 min. Homoeostatic Model Assessment (HOMA) was calculated.

Results: Adrenal insufficiency was not present in survivors. Interestingly, baseline serum cortisol levels were higher in survivors after unilateral adrenalectomy (mean 503 nmol/l) ($N = 46$) than in survivors with both adrenals intact (mean 393 nmol/l, $P = 0.002$) ($N = 52$), and than in controls (mean 399 nmol/l, $P = 0.013$) ($N = 49$). After correcting for age, sex and use of oral oestrogens, unilateral adrenalectomy was independently associated with elevated baseline cortisol and ACTH levels. Baseline cortisol levels were positively associated with triglycerides ($P < 0.001$), LDL-C ($P = 0.004$), apolipoprotein-B ($P < 0.001$) and HOMA ($P = 0.008$).

Conclusions: No adrenal insufficiency was observed in survivors of nephroblastoma and neuroblastoma. Survivors treated with unilateral adrenalectomy had relatively high basal cortisol and ACTH levels, indicating a higher central setpoint of the hypothalamic-pituitary-adrenal

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axis. This higher setpoint was associated with lipid concentrations and insulin resistance and can therefore influence the cardiovascular risk profile in long-term survivors of nephroblastoma and neuroblastoma.

1. Introduction

Over the past decades, childhood cancer survival rates have increased significantly. Approximately 75% of children diagnosed with cancer are cured and become long-term survivors. For children diagnosed with nephroblastoma or neuroblastoma 5-year survival is approximately 84% and 64%, respectively. Increased long-term survival has led to increasing absolute numbers of survivors: to date one in 640 young adults is a childhood cancer survivor.[1] Therefore the recognition of late effects has become more relevant. In nephroblastoma and neuroblastoma survivors, especially those treated with radiotherapy, the risk for developing late adverse events like second malignant neoplasms and pulmonary, orthopaedic and cardiovascular events, musculoskeletal late effects, cardiac toxicity, reproductive health problems and renal dysfunction is significant.[2–4] Due to poor survival, reports on late effects in intensively treated long-term neuroblastoma survivors are mainly based on case series and small cohorts.

Although endocrine sequelae are the most common late effects,[5–15] little is known about the long-term endocrine effects in survivors of nephroblastoma or neuroblastoma. Increased mortality rates as compared to the general age-matched population have been reported in childhood cancer survivors, which are partly related to the above-mentioned documented late effects.[16] However unexpected deaths occur and to date it is unknown whether adrenal insufficiency following surgery, radiotherapy and/or chemotherapy for nephroblastoma or neuroblastoma is an important denominator of this excess mortality rate later in life. Abdominal surgery is part of the treatment for nephroblastoma and neuroblastoma. In the majority of nephroblastoma patients, unilateral total nephrectomy, often including unilateral adrenalectomy, is performed. In neuroblastoma patients, adrenalectomy is performed when the tumour is located in the adrenal gland. Bilateral adrenalectomy is associated with high morbidity and mortality rates as a consequence of adrenal insufficiency.[17,18] It is unknown whether adrenal function after unilateral adrenalectomy declines over time by ageing, especially in survivors who were also treated with chemotherapy or local radiotherapy. We hypothesised that a subset of neuroblastoma and nephroblastoma survivors has a subnormal adrenal function and therefore performed a study on the influence of administered treatment on adrenal function in long term nephroblastoma and neuroblastoma survivors. Additionally, to evaluate the possible altered effect of the hypothalamic-pituitary-adrenal (HPA) axis on the metabolic status in these survivors, we assessed the influence of cortisol on lipids and insulin resistance parameters.

2. Methods

2.1. Patients

All long-term ($\geqslant$5 years after cessation of treatment) adult survivors of childhood nephroblastoma and neuroblastoma, treated between 1961 and 2004 in the Erasmus MC-Sophia Children's Hospital are followed prospectively at the Late Effects Registration outpatient clinic. They were invited to participate in this cross-sectional study. Informed consent was obtained according to the Helsinki declaration[19] and the study was approved by the local medical ethical committee.

Of the 88 adult long-term survivors of nephroblastoma who were alive and currently living in The Netherlands, 67 participated, six were lost to follow-up, 13 refused to participate and two survivors were not able to visit the outpatient clinic at the appointed time interval. Adult survivors with neuroblastoma stage 4s who did not receive surgery, radiotherapy or chemotherapy were excluded from this study. Of the 50 eligible neuroblastoma survivors, 36 survivors participated, five were lost to follow-up, six refused to participate and three females were pregnant at the time of the study. Information on disease and treatment was obtained from our local database and medical records. Data regarding (partial) unilateral adrenalectomy were obtained from pathology reports. As to date limited normal values for young adults are available, we recruited a control group, consisting of siblings, friends or neighbours, preferably of the same sex and within an age range of 5 years of their related survivor. This group was designed as a socio-demographically similar comparison population. Information regarding smoking status and socio-economic status (defined by the highest level of educational attainment) was collected using a questionnaire. Height was measured to the nearest millimetre using a Harpenden Stadiometer and weight was measured without shoes and clothes but in underwear to the nearest 0.1 kg with a standard clinical balance. Body mass index (BMI) was calculated as weight in kilograms divided by the squared length in metres. Survivors and controls participated in this study from October 2009 until March 2011.