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Obesity in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

THESE

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Rapport de synthèse

Le traitement des leucémies aiguës chez l'enfant représente un des succès de la médecine moderne avec des taux de guérison avoisinant les 80% ce qui implique la nécessité de suivre les effets secondaires à long terme des traitements chez cette population de patients. Récemment plusieurs études internationales ont relevé une prévalence plus importante de surpoids et d'obésité chez les enfants traités pour une leucémie aiguë. L'origine de ce processus reste incertaine : aux effets secondaires bien connus et décrits des traitements (stéroïdes et radiothérapie) semblent s'ajouter des facteurs génétiques, familiaux (age, BMI au diagnostic, BMI parents et fratrie), environnementaux.

L'objectif de ce travail est d'estimer la prévalence et les facteurs de risque pour le surpoids et l'obésité chez les enfants traités et guéris d'une leucémie aiguë en Suisse romande et de comparer ces résultats à ceux d'études internationales. Pour répondre à ces questions nous avons inclus 54 patients (40 de Lausanne et 14 de Genève) traités pour une leucémie aiguë. Seuls les enfants à 5 ans de leur première rémission clinique, sans atteinte du système nerveux central, testiculaire ou médullaire et traités par chimiothérapie seule sont retenus. Leur poids, taille sont enregistrés durant les phases précises de traitement (au diagnostic, à la rémission, fin de consolidation, milieu-maintenance et en fin de traitement) puis annuellement jusqu'à 12 ans post fin de traitement. Le BMI (kg/m2) et sa déviation standard BMI-SDS (spécifique pour l'age et le sexe) pour les patients et leurs parents sont calculés selon les valeurs internationales (IOTF) respectivement BMI-SDS >1.645 ($p<0.05$) pour le surpoids et > 1.96 ($p<0.025$) pour l'obésité.

Les résultats de ce travail confirment une prévalence double de surpoids (30% versus 17%) et quadruple d'obésité (18% versus 4%) au sein de la population d'enfants traités pour une leucémie aiguë comparées à la population suisse standard. Les facteurs de risque impliqués sont le BMI initial au diagnostic et le BMI maternel contrairement à l'age, sexe, stéroïdes et au BMI paternel.

Ces données confirment une prévalence significative d'enfants en surpoids/obèses au sein de cette population avec des résultats similaires à ceux retrouvés dans des études internationales récentes. Les facteurs de risque identifiés semblent plutôt liés à l'environnement familial qu'aux traitements. Ces constatations pourraient être le résultat d'interactions complexes entre ''le background génétique'', les facteurs environnementaux, les habitudes socioculturelles (activité physique, status nutritionnel) paramètres non évalués dans cette revue. Des études plus larges, prospectives sont nécessaires pour clarifier les rôles des différents facteurs de risque et de leurs interactions ; celles-ci devraient inclure des données génétiques (LEPR), taux de leptine, activité physique et le status nutritionnel. Enfin, l'identification des patients à risque est cruciale afin de prévenir les effets secondaires cardio-vasculaires, métaboliques bien connus liés au surpoids et à l'obésité.

Obesity in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

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Background. Childhood acute lymphoblastic leukemia (ALL) with current cure rates reaching 80% emphasizes the necessity to determine treatment related long-term effects. The present study examines the prevalence of and the risk factors for overweight and obesity in a cohort of ALL survivors treated and living in the French speaking part of Switzerland. ***Methods.*** In this retrospective two-center study, height and weight of 54 patients diagnosed with ALL in first complete remission and treated with chemotherapy only were recorded at specified time points during treatment and off-therapy. Body mass index (BMI) and its age- and gender-adjusted standard deviation score (BMI-SDS) were calculated for the patients and their parents separately. Overweight and obesity were defined by a threshold of BMI-SDS >1.645 and BMI-SDS >1.96, respectively. ***Results.*** At last follow-up, 16 (30%) of the 54 survivors were overweight and 10 (18%) were obese. The off-treatment period was most at risk with 11 of the 16 becoming overweight and 9 of the 10 becoming obese during that period. Overweight/obesity at diagnosis and abnormal maternal BMI were significantly associated with abnormal weight at follow-up, while age at diagnosis, gender, cumulative dose of steroids and paternal BMI showed no association. ***Conclusions.*** Consistent with published evidence from other regions of the developed and developing world, there is a significant prevalence of obesity in young ALL survivors in the French speaking part of Switzerland. Factors significantly associated with this late effect were mostly related to the familial background rather than to the treatment components. Pediatr Blood Cancer

Key words: childhood acute lymphoblastic leukemia; obesity; overweight; prevalence; risk factors

INTRODUCTION

Treatment of childhood acute lymphoblastic leukemia (ALL) is one of the success stories of modern medicine with current cure rates reaching 80% [1]. With the growing number of survivors, it becomes increasingly important to understand treatment-related long-term effects. In North America, Western Europe, Australia, New Zealand, some parts of the Middle East and in rapidly developing countries such as China, overweight and obesity are now more important forms of malnutrition than undernutrition in the general pediatric population [2,3]. Zee and Chen [4] provided the first report of a potential association between obesity and ALL therapy in 1986. Since then other studies [5–11] showed an association between patients undergoing ALL therapy and excessive weight gain. Nevertheless, the etiologic roles of some patient characteristics (e.g., age, gender and body mass index (BMI kg/m^2) at diagnosis) and of different treatment components (e.g., the dose of cranial radiotherapy (CRT), the type of steroids and the cumulative dose of steroids) in the development of overweight/obesity remain unclear [8,9]. Furthermore, recent studies [10,11] point out a strong correlation between some of the patient's familial characteristics and the risk of long-term excessive weight gain in this cohort.

The objective of this retrospective study was to assess the prevalence of, and the risk factors for overweight and obesity in a representative cohort of ALL survivors treated and living in the French speaking part of Switzerland. Height and weight measurements were done at specified time points during treatment and follow-up periods in order to determine the most sensitive period for abnormal weight gain. Several potential risk factors were examined, including the cumulative steroid doses and both the parental and personal growth parameters.

METHODS

Patients were drawn from a previously identified group of 60 children diagnosed with precursor B-cell ALL in the French speaking part of Switzerland (Geneva and Lausanne) between 1990 and 2000 [12]. Only patients without initial central nervous system or testicular involvement, treated without CRT and in first complete remission from at least 5 years after diagnosis were included. Patients with trisomy 21, Prader–Willi or Beckwith–Wiedemann syndromes were excluded from the study. The study protocol was reviewed and approved by the respective Institutional Review Boards. From the initial 60 eligible patients, 4 were excluded because they were lost during the follow-up period and 2 were excluded because of central nervous system relapse. Of the remaining 54 patients, 40 were from Lausanne and 14 from Geneva. Patient's ages at diagnosis of ALL ranged from 2 to 12 years, with a median of 3.5 years.

ALL treatment was administered according to a series of subsequent protocols from the Paediatric Oncology Group (POG): POG 8602, POG 9201, POG 9005/06, POG 9405/06, POG 9605, and POG 9904/05/06. Treatment details have been published elsewhere [13]. Briefly, all protocols included a 4 weeks induction with prednisone (40 mg/m^2/day) or dexamethasone (6 mg/m^2/day) as well as 5–7 days blocks of steroids at different time points during consolidation, intensive continuation or maintenance. Patients were followed annually up to 12 years after completion of therapy, with a median follow-up of 6 years. In order to determine a critical period for excessive weight gain, height and weight were recorded and BMI and its standard deviation score (defined as BMI-SDS) computed at specific and specified time points: diagnosis, complete remission, end of consolidation, mid-maintenance, end of treatment and annually during follow-up. Patient's heights and weight were retrospectively extracted from the medical charts. Both BMI and BMI-SDS were computed and scored according to the International Obesity Task Force (IOTF) criteria [14,15] overweight being defined by a gender- and age-specific BMI-SDS > 1.645 (exceeding 95th percentile) and obesity by a gender- and age-specific BMI-SDS > 1.96 (>P97.5). In addition, the BMI and BMI-SDS of the parents were calculated from self-reported data. Parents were

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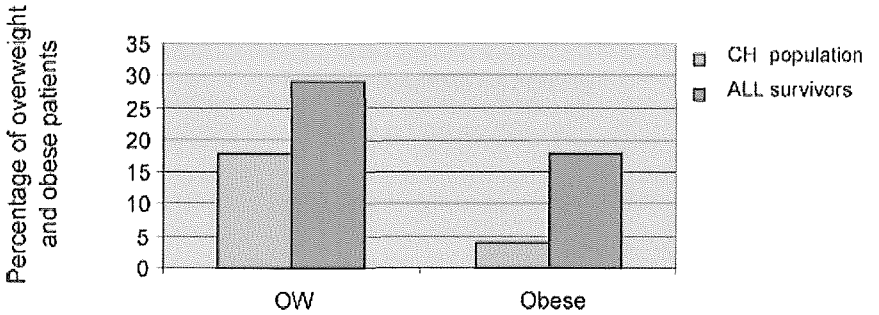

Fig. 1. Overweight and obesity in ALL survivors compared to the general pediatric Swiss population. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

considered either normal (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2) or obese (BMI > 30 kg/m^2).

For statistical analysis, data on patient outcomes were locked on May 31, 2005. To assess and compare the overweight and obesity rates in the different groups, cumulative incidences and their 95% confidence intervals (95% CI) were calculated comparably to the Kaplan–Meier method. Univariate analysis of the influence of different variables on overweight and obesity was performed applying the log-rank-test. Continuously measured potentially influencing variables were dichotomized or categorized according to quartiles, where applicable. Two-sided tests were used throughout, and P-values below 0.05 were considered significant. No correction for the multiple comparisons performed in this exploratory study was applied. S-PLUS 6.0 (Insightful Corp., Seattle, WA) software was used.

RESULTS

At last follow-up, nearly half of the ALL survivors had excessive weight: 16 (30%) of the 54 patients were overweight and 10 (18%) obese. These numbers contrast with the rates observed in the general Swiss population of comparable age and gender, 17% and 4%, respectively (Fig. 1) [19]. Considering the entire observation period from the diagnosis until the last control, a total of 32 patients (59%) exceeded at least once the overweight (N = 18, 33%) or the obesity (N = 14, 26%) threshold.

The majority of the overweight survivors (11 of 16) and nearly all obese survivors (9 of 10) developed excessive weight gain during the follow-up period. During therapy, 17% of the patients (9/54) became overweight. At the end of consolidation 13% of the patients (7/54) became obese as a result of the steroids. This abnormal weight gain resolved spontaneously later on in the course of treatment in most cases (Fig. 2). There was no effect of the cumulative dose of steroids on the incidence of overweight or obesity in the survivors at follow-up (Fig. 3).

Two risk factors were associated with the development of abnormal weight gain in a statistically significant way. The first was an abnormal BMI-SDS at diagnosis of ALL. While only 14 (30%) of the 47 survivors having a normal BMI-SDS became obese in the long term, 5 of the 7 initially overweight or obese children reached the obesity threshold during the follow-up period ($P < 0.004$; Fig. 4). The second was maternal BMI. While only 5 (20%) of the 24 children with normally weighting mothers became overweight or obese, 4 of the 5 with overweight or obese mothers were fulfilling the obesity threshold ($P = 0.021$; Fig. 5). Paternal BMI was not significantly associated with the patient's risk for overweight at follow-up: 7 (33%) of the 21 children with normal weighting fathers, compared to 5 of the 7 with overweight or obese fathers were overweight or obese at follow-up ($P = 0.077$). Gender and age at diagnosis had no significant association with the development of overweight or obesity (data not shown).

DISCUSSION

As in other countries, we found a high prevalence of overweight and obesity in our population of ALL survivors with almost double and fourfold rates compared to the standard Swiss children of similar age and sex, respectively. These results are comparable with the one from international studies [6,7,8,16–18] but the treatment exposure consisted mostly of chemotherapy and CRT. Oeffinger et al. [6], in a recent Childhood Cancer Survivor Study (CCSS) reported on 1,765 survivors of childhood ALL and a comparison group of 2,565 siblings. They found respectively a prevalence of 28% and 17% of overweight and obese patients. Kourti et al. [18] studied the frequency of overweight and obesity in a cohort of 52 survivors of ALL. They concluded that 48% were overweight and 8% were obese. Sklar et al. [8] reported on a prevalence of 30% of obese patients in their cohort of 126 survivors of childhood ALL,

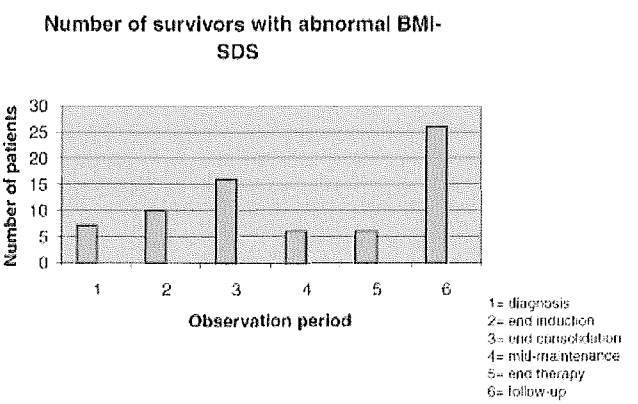

Fig. 2. Number of survivors with abnormal BMI-SDS during the observation period. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

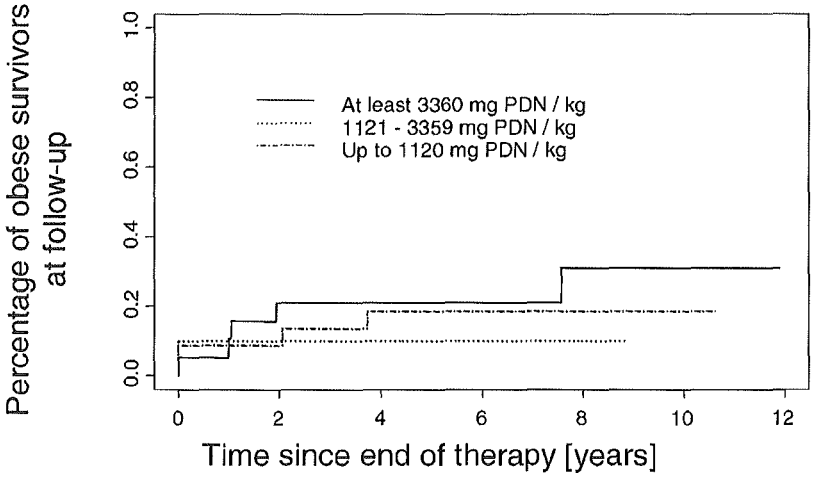

Fig. 3. Effect of cumulative steroid dose: $P > 0.050$.

knowing that most of them were undergoing cranial radiotherapy and chemotherapy (88/126).

Different hypotheses can be discussed to explain these findings. Abnormal weight gain could be the result of the drugs used to treat ALL, especially steroids, which are known to increase body fat. Although we observed the expected excessive weight gain after induction/consolidation, the majority of patients returned to a normal weight and BMI later in the course of therapy, a finding clearly speaking against a long-lasting effect of the steroids. Interestingly, the majority of our patients being overweight or obese at follow-up developed their abnormal weight gain after the end of therapy, another argument against directly steroid-related effects. Cranial irradiation has been clearly linked to a series of late events in ALL survivors, including overweight and obesity. Former late effects studies in ALL survivors demonstrated that CRT was a major risk factor for overweight/obesity in the long-term and discussed several hypotheses and mechanisms [8,9] Brennan et al. [9] suggested that radiation damage to hypothalamic neurons controlling eating behaviors and leptin resistance were mainly involved in the development of late excessive weight gain in this population. However, due to small sample sizes and lack of optimal comparison groups, these hypotheses remain extremely speculative and need larger prospective cohorts to be confirmed.

If not, or not only therapy related, overweight and obesity in long-term ALL survivors could be associated with the genetical, or more broadly speaking the familial background of the patients. We looked therefore at patient's own BMI at ALL diagnosis and parental BMI as possible relevant markers for this background. Although based on a relatively small patients and parents population, our findings point to a statistically significant and clinically relevant impact of the patient's own body constitution represented by his/her BMI at ALL diagnosis and the maternal BMI; paternal BMI showed a tendency for association. "Familial" is of course broader than "genetical" and includes potential interactions between an individual genetical condition and the family's environment, that is, type of diet, physical activity a.o. Furthermore, this "familial background" will be able to interact with the different components of a given therapy. Recent studies [10,11] explored those interactions: Shaw et al. found a significant maternal predisposition where 59% of their obese female survivors had

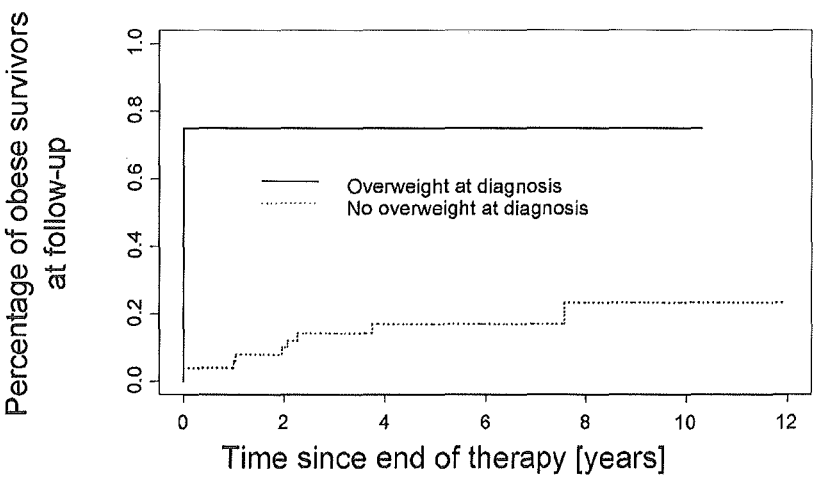

Fig. 4. Effect of overweight at diagnosis: $P < 0.050$.

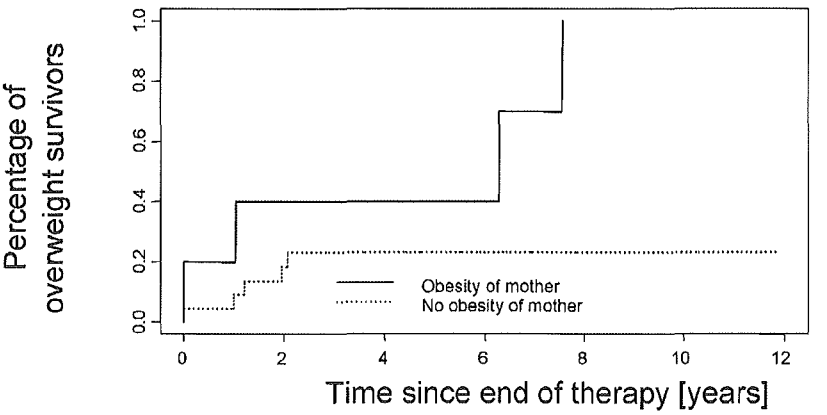

Fig. 5. Overweight, effect of maternal obesity.

obese mothers while only 14% of them had obese fathers. Ross et al. reported a high correlation between the LEPR (leptin receptor gene) polymorphism and obesity in female ALL survivors being homozygous for the Arg genotype and having undergone CRT. Comparably to our study, Shaw et al. [11] pointed out the role of maternal BMI as risk factor for obesity in ALL survivors: a larger percentage of female subjects whose mothers were obese became obese themselves, but only if treated with CRT. A retrospective study conducted by Razzouk et al. [21] concluded that patients fulfilling the overweight or obese threshold at diagnosis were the most at risk of becoming obese when reaching adult height. These results are of particular interest because there were no significant differences in the BMI rates between patients having undergone CRT and those who received chemotherapy only. This study also showed that the familial weight pattern has a deeper impact on the survivors BMI than treatment components as CRT. These data highlight the need to further investigate the complex interactions between genetic background, environmental factors and treatment components.

There are some caveats in interpreting the results of the current study. First, the small number of ALL survivors included as well as the retrospective study design could be responsible for the lack of statistical significance of certain risk factors, for example, the impact of the cumulative steroid dose. Second, the BMI of the mothers and fathers have been computed from self-reported heights and weights, which are both subject to a degree of imprecision. Furthermore, it could be argued that BMI and BMI-SDS are not the best means for estimating overweight and obesity, because they do not distinguish fat mass from lean mass. More precise methods like dual X-ray absorptiometry should be used to overcome this difficulty, but they are both time-consuming and expensive. Therefore, BMI remains the standard measure of obesity in the majority of population based studies. A third caveat is the BMI-SDS reference values used as cut-offs for overweight and obesity in children. Two options are currently available, from the US Centre for Disease Control and Prevention (CDC) and from the IOTF. The overall performance of the CDC reference values is superior. Nevertheless we calculated the z-scores in the present study according to the normative data from IOTF (Cole et al.), since international studies typically use the IOTF criteria and we wished to make comparisons with these studies. Fourth and finally, data on genetic [20,22] and anthropometric data, detailed information on ethnicity, nutritional habits and physical activity were not available in the present study. Our findings are nevertheless important because they confirm the high prevalence of overweight and obesity even in a homogenous group of survivors of childhood B-precursor ALL treated with chemotherapy only. By computing BMI-SDS at very specific time-points during and off therapy we found that the majority of patients developed excessive weight gain during the follow-up period.

Increased rates of obesity in this population may be the result of complex interactions between specific genetic backgrounds, as indicated by patient and maternal baseline BMIs, as well as environmental factors, such as specific treatment components or socio-cultural habits (physical activity, nutritional status) not tested in the present study. Larger prospective cohort studies are needed to clarify the individual roles and interactions of these risk factors in a given patient. Specifically future studies should include data on LEPR and other gene polymorphisms, levels of leptin, physical activity, dietary habits, nutritional status, as well as BMIs of the survivors, parents and siblings. Early detection of patients at risk and early implementation of preventive interventions (enhancement of physical activity, appropriate diet, etc.) are important for the effective prevention of obesity which, in turn, may reduce the risk of the metabolic syndrome and its long-term deleterious cardiovascular consequences.

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