ISSN 2082-369X

Przegląd Medyczny Uniwersytetu Rzeszowskiego i Narodowego Instytutu Leków w Warszawie
Rzeszów 2011, 2, 174–177

Szymon Skoczen[1], Miroslaw Bik-Multanowski[2], Walentyna Balwierz[3], Jacek J. Pietrzyk[2]

The rs9939609T>A polymorphism of the FTO gene and overweight in survivors of ALL

Polimorfizm rs9939609T>A genu FTO a występowanie nadwagi u osób wyleczonych z ALL

[1] Chair of Clinical Immunology and Transplantation, Jagiellonian University Krakow, Poland
[2] Chair of Pediatrics, Jagiellonian University Krakow, Poland
[3] Department of Oncology and Hematology, Jagiellonian University Krakow, Poland

ABSTRACT

Background: Overweight is a serious late complication of acute lymphoblastic leukemia (ALL). The aim of the study was to assess the role of the rs9939609T>A polymorphism of the FTO gene in development of overweight in ALL survivors.

Methods: Genotyping for the above genetic variant was performed in 191 patients, who completed treatment for ALL.

Results: The presence of the rs9939609A allele correlated with post-treatment overweight incidence in patients receiving cranial radiotherapy, whereas the rs9939609T allele seemed to protect against overweight development.

Conclusion: The rs9939609T>A variant can influence overweight risk in selected patients with ALL.

Keywords: overweight, leukemia, genetic predisposition, population, FTO gene, cranial irradiation

STRESZCZENIE

Wstęp: Nadwaga jest poważnym późnym powikłaniem ostrej białaczki limfoblastycznej (ALL). Celem niniejszego badania była ocena roli polimorfizmu rs9939609T>A genu FTO w rozwoju nadwagi u pacjentów wyleczonych z ALL.

Metody: Genotypowanie w kierunku powyższego wariantu genetycznego zostało przeprowadzone u 191 pacjentów, którzy zakończyli leczenie z powodu ALL.

Wyniki: Obecność allela rs9939609A korelowała z występowaniem nadwagi u pacjentów leczonych radioterapią czaszki, podczas gdy allel rs9939609T wykazywał działanie protekcyjne w stosunku do rozwoju nadwagi.

Wnioski: Wariant genowy rs9939609T>A może wpływać na ryzyko wystąpienia nadwagi u pacjentów z ALL.

Słowa kluczowe: nadwaga, białaczka, predyspozycje genetyczne, populacja, gen FTO, radioterapia czaszki

Introduction

The obesity epidemic is responsible for a substantial economic burden. It is already responsible for 2–8% of health costs and 10–13% of deaths in developed countries [1]. Being overweighed is a well-established risk factor for many chronic diseases, such as diabetes, hypertension and cardiovascular events.

Survivors of pediatric acute lymphoblastic leukemia (ALL) have increased risk of developing obesity [2, 3]. However, treatment related, as well as inherited risk factors for overweight are poorly understood. Among others, cranial radiotherapy (CRT) has been suggested as one of such risk factors [3]. On the other hand genetic variations in the fat mass and obesity associated gene (FTO) were also linked to the obesity phenotype [4, 5]. Therefore, the aim of the study was to assess the role of rs9939609T>A polymorphism of the FTO gene in overweight development in patients treated for ALL.

Methods

A group of 191 persons (99 females/93 males) aged 4–28 years (median 14) who have completed ALL therapy, were ascertained in Department of Oncology and Hematology, Jagiellonian University. The patients started treatment from 6/11/1979 through 8/24/2005. The age at diagnosis was 1–18 (median 4.6) years. Median time from completion of treatment was 4.7 years.

ALL therapy was conducted according to subsequent revisions of modified BFM (147 patients) and New York (44 patients) regimens [6, 7, 8]. A group of 137 (72%) patients received less intensive treatment (BFM for standard/intermediate risk patients), whereas 54 (28%) were treated with more intensive protocols (New York and BFM for high risk patients, second protocol for relapse). Prophylactic and/or therapeutic CRT was introduced in 93 patients according to treatment protocols, in doses 12 to 24Gy (median 18.2Gy). The majority of patients who were treated with more intensive protocols (94.4%) received CRT.

Blood samples were collected at routine outpatient visits; DNA was extracted from peripheral blood leukocytes. Subsequently, genotyping for polymorphism rs9939609T>A of the FTO gene was performed by means of PCR technique followed by direct sequencing. The primer sequences were as follows: forward – tctaggttccttgcgactgc and reverse – gttaatggcttcagggtaccagc.

The Body Mass Index (BMI) and BMI percentile were calculated by means of on-line BMI calculators (www.cdc.gov/healthyweight/assessing/bmi/index.html and www.halls.md/body-mass-index/bmi.htm). Patients with BMI percentile ≥85 were classified as overweighed.

The correlations of the FTO gene variant rs9939609T>A and overweight in ALL survivors were analyzed. Descriptive statistics, odds ratio (OR) with 95% confidence interval and the Fisher's exact test were used.

Local ethics committee accepted the study protocol. All parents and adolescent patients signed informed consent before blood sample collection.

Results and Discussion

The median BMI percentiles at diagnosis and after treatment were 51.2 and 60.8 respectively. Only slight increase of overweight frequency was observed in the entire studied population (18.8% of children at diagnosis and 20.9% after treatment). However, if analyzed in subgroups, the overweight frequency visibly increased in the cohort of patients treated without cranial radiotherapy and with less intensive protocols (18.4% vs. 27.6% and 16.1% vs. 23.4% respectively). On contrary, it decreased in the groups of patients receiving cranial radiotherapy and in patients treated with more intensive protocols (19.3% vs. 14% and 25.9% vs. 14.8% respectively).

No correlation of the FTO gene polymorphism rs9939609T>A with overweight before treatment was found for the entire studied group and for the subgroups. On contrary, increased frequency of the rs9939609A variant was detected after treatment in overweighed patients who received cranial radiotherapy (OR 2.59; 95% CI 1.11-6.02; $p = 0.04$). Details on genotyping are presented in Table 1.

The 9939609T>A polymorphism of the FTO gene has recently been suggested as additional factor contributing to the development of obesity. As overweight is a known treatment-related complication in patients with leukemia, one could expect that presence of the above polymorphism increases risk of overweight development in these patients. The results of our study seem to partially confirm this hypothesis. Although we assessed a relatively large group of leukemia survivors, we were not able to detect the expected correlation in the entire studied group. However, in patients who were treated with additional cranial radiotherapy, the presence of 9939609A allele correlated significantly with overweight after leukemia treatment.

Cranial irradiation has the potential to cause hypothalamic damage, which in turn can affect the amount of body fat tissue. Our results show, that combination of cranial radiotherapy and of presence of the 9939609A variant significantly increases the risk of development of overweight in patients with ALL. The cohort of patients receiving more intensive treatment overlapped with the CRT group, what could explain the presence of similar trends in the "more intensive" patients (Table 1). Interestingly, although the number of patients with overweight after treatment is relatively low in the "cranial irradiation" and "more intensive" groups (what is probably an incidental finding), a trend indicating protective role of the 9939609T variant against overweight development is visible (Table 1). The above protective effect of the 9939609TT (wild type) genotype remains to be confirmed in further studies as it could be of practical interest for clinicians taking care of children with ALL.

In conclusion, as overweight is a well-established risk factor for many chronic diseases, genotyping for the rs9939609T>A polymorphism of the FTO gene might be useful in predicting increased (in AA homozygotes) or lower (in TT homozygotes) risk of overweight development in patients with ALL.

References

1. Branca F, Nikogosian H, Lonstein T. *The challenge of obesity in the WHO European Region and the strategies for response*. WHO Europe 2007; (www.euro.who.int/document/E90711).
2. Gregory JW, Reilly JJ. *Body composition and obesity*. In: Wallace H, Green D, editors. *Late effects of childhood cancer*. London: Arnold; 2004; p145–161.
3. Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. *Obesity and hypertension among children after treatment for acute lymphoblastic leukemia*. Cancer 2007;110:2313–2320.

Table 1. Overweight development and genotyping for the rs9939609T>A polymorphism

Tabela 1. Rozwój nadwagi a genotypowanie polimorfizmu rs9939609T>A

	Cranial radiotherapy			**No cranial radiotherapy**			**More intensive treatment protocol**			**Less intensive treatment protocol**		
	Entire group (93)	Overweight before treatment (19.3% of patients)	Overweight after treatment (14% of patients)	Entire group (98)	Overweight before treatment (18.4% of patients)	Overweight after treatment (27.6% of patients)	Entire group (54)	Overweight before treatment (25.9% of patients)	Overweight after treatment (14.8% of patients)	Entire group (137)	Overweight before treatment (16.1% of patients)	Overweight after treatment (23.4% of patients)
TT (number of cases)	46	12	4	56	10	15	22	7	1	80	15	18
TA (number of cases)	23	2	2	23	6	8	16	3	3	30	5	7
AA (number of cases)	24	4	7	19	2	4	16	4	4	27	2	7
Allelic frequency (rs9939609A allele)	0.38[a]	0.27[b]	0.61[ab]	0.31	0.27	0.29	0.44	0.39	0.69	0.31	0.2	0.33
Statistical differences	[a]OR 2.59; 95% CI 1.11-6.02; **p=0.041** [b]OR 4.16; 95% CI 1.42-12.19; **p=0.001**			No significant differences			No significant differences			No significant differences		

4. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. *A common variant in the FTO gene is associated with Body Mass Index and predisposes to childhood and adult obesity*. Science 2007;316:889–894.
5. Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobson P, Carlssson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Herckberg S, Le Stunff C, Bougneres P, Kovacs P, Marre M, Balkau B, Cauchi S, Chevre JC, Froguel P. *Variation in FTO contributes to childhood obesity and severe adult obesity*. Nat Genet 2007;39:724–726.
6. Radwanska U, Michalewska D, Armata J, Balwierz W, Boguslawska-Jaworska J, Cyklis R, Derulska D, Kolecki P, Lastowska M, Newecka-Samol T. *Acute lymphoblastic leukemia therapy in Poland*. Folia Haematol Int Mag Klin Morphol Blutforsch. 1989;116:199–210.
7. Radwanska U, Michalewska D, Kolecki P, Armata J, Balwierz W, Boguslawska-Jaworska J, Chybicka A, Cyklis R, Kowalczyk J, Ochocka M. *Standard and intermediate risk acute lymphoblastic leukemia in Poland. A report of the Polish Children*. Leukemia/Lymphoma Study Group. Acta Paediatr Jpn 1995;37:31–36.
8. Balwierz W, Moryl-Bujakowska A, Skoczen S, Pawinska K, Balcerska A, Ploszynska A. Chybicka A, Dobaczewski G, Juszczak K, Wachowiak J, Derwich K, Kowalczyk J, Wisniewska-Slusarz H, Matysiak M, Krauze A, Rokicka-Milewska R, Pawelec K, Sonta-Jakimczyk D, Luszczynska A, Tomaszewska R, Wysocki M, Styczynski J, Swiatkiewicz V. *Advances in the treatment of children with high risk acute lymphoblastic leukemia (ALL) treated with modified „NEW YORK" protocols between 1987 and 2002*. Przegl Lek. 2003;60(Suppl.5):13–16.

Adres do korespondencji / Mailing address:
Miroslaw Bik-Multanowski,
Chair of Pediatrics, Jagiellonian University,
ul. Wielicka 265, 30-663 Krakow, Poland
e-mail: m.bik@wp.pl,
Phone: +48 602 55 91 31; Fax: +48 12 658 44 46