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A tagging polymorphism in fat mass and obesity-associated (*FTO*) gene is associated with sepsis status in children

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Abstract

Introduction: Sepsis is one of the most common causes of death in patients admitted to intensive care units (ICUs). The development of sepsis is significantly influenced by genetic predisposition. In this study, we highlight a potential association between a variant of the fat mass and obesity-associated (*FTO*) gene and risk of sepsis in children and adolescents.

Methods: We investigated a first-intron tagging *FTO* polymorphism (rs17817449) by comparing a severe condition (SC) group, comprising 598 paediatric patients (ages 0–19 years) admitted to an ICU with fever, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, or multiple organ dysfunction syndrome (MODS), with a control group consisting of 616 healthy young adults.

Results: We observed a lower prevalence ($p < 0.01$; OR = 0.59, 95% CI = 0.39–0.87) of the *FTO* TT genotype in febrile and SIRS patients compared to patients with severe illness. There was a borderline trend towards a lower prevalence of the *FTO* TT genotype in the control group compared to the SC group ($p < 0.09$, OR = 0.81, 95% CI = 0.62–1.06).

Conclusions: Our findings suggest that rs17817449, a common *FTO* polymorphism, may be a predictor of sepsis in paediatric patients, and that higher body weight is protective against this clinical complication.

Keywords: child; obesity; sepsis; genotype, genetic predisposition to the disease.

What is new? What is important?

A lower body mass index (BMI) is associated with the risk of sepsis. Variants within the fat mass and obesity-associated (*FTO*) gene are the strongest genetic predictors of BMI. Our results indicate that the *FTO* genotype rs17817449 is associated with a higher BMI and may mitigate severe sepsis in paediatric patients admitted to ICUs.

INTRODUCTION

Sepsis is one of the most common causes of death in patients admitted to intensive care units (ICUs). The definitions of sepsis and septic shock, which focus on the inflammatory response of the host, have remained unchanged since they were first published in 1991 [1,2]. In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as a "*life-threatening organ dysfunction caused by a deregulated host response to infection*," and septic shock as a "*subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality*" [2,3]. The above definition of sepsis currently applies

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to the adult population. However, recommendations have been made to redefine paediatric sepsis in alignment with the adult Sepsis-3 definition and organ dysfunction scoring [4,5].

Early initiation of intensive care can significantly reduce sepsis complications. In 2013, a staging system based on the Predisposition, Insult, Response, and Organ dysfunction (PIRO) concept was proposed to improve the staging of sepsis states [6]. The model helps clinicians predict the risk of sepsis development, infection severity, and death. It is also used to stratify patients based on predisposing factors with the aim of improving sepsis management and delivering more accurate prognoses. However, numerous other factors contribute to a patient's predisposition to sepsis and the severity of the ensuing septic state [7].

As confirmed by several studies, genetic predisposition plays a significant role in sepsis development [8–11]. Despite some disagreement, the evidence suggests that a higher body mass index (BMI) is an important predictor of lower mortality in sepsis cases [12,13]. It is estimated that approximately 30 to 50% of the differences in BMI are genetically determined. Common single nucleotide polymorphisms (SNPs) within the fat mass and obesity-associated (*FTO*) gene (ID: 79068, OMIM: 610966) are the strongest known genetic determinants of BMI [14], exerting a consistent effect across different age subgroups [15]. Although the exact mechanism remains unclear, *FTO* seems to influence BMI through epigenetics, encoding a nucleic acid demethylase [16].

Considering the link between BMI and the risk of sepsis, and that *FTO* is the strongest genetic predictor of BMI, we sought to analyse the potential association between the tagging variant of *FTO* and risk of sepsis in children and adolescents.

MATERIALS AND METHODS

STUDY SUBJECTS

We retrospectively enrolled 598 consecutive paediatric patients [9,17,18], aged 0 to 19 years (325 boys, 273 girls), who were admitted to the paediatric intensive care unit at University Hospital Brno for at least 24 h. Inclusion criteria were as follows: fever, defined as body temperature >39°C or >38.5°C measured consecutively on two occasions at least 6 h apart; systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, or multiple organ dysfunction syndrome (MODS) based on consensus criteria modified for paediatric patients [4,19]; signed informed consent by parents or legal guardians; and successful genotyping of the gene variant of interest.

Consecutive patients were enrolled from September 2003 to December 2011. Their clinical status was monitored daily by an experienced physician.

The control group, consisting of 616 healthy individuals (365 male and 251 female) between the ages of 26 and 40, was chosen as a random subsample of the Czech post-MONICA WHO study [20,21].

The study was approved by the Institutional Review Board of the University Hospital Brno in accordance with the 1964 Declaration of Helsinki (protocol code 5684-FNBr-02/12/2002).

Hereinafter, we refer to patients generally as the patient group (PG), febrile and/or SIRS patients as the FS group, patients with one or more of the following severe conditions – sepsis, severe sepsis, septic shock, or MODS – as the SC group, and healthy individuals as the control group (CG).

MEASUREMENTS AND VARIABLES

Body weight was measured using a calibrated electronic weighing scale. Height was measured to the nearest 0.5 cm. Weight and weight-for-height ratio values were calculated using standard growth charts used in the Czech Republic [22]. We consulted the Compendium of Paediatric Auxology (a Czech publication) to evaluate weight-for-age, height-for-age, and weight-for-height percentiles.

1) DNA was isolated from EDTA blood using a slightly modified salting-out method. The *FTO* variant rs17817449 was analyzed using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique [20]. Briefly, 5′ GGT GAA GAG GAG GAG ATT GTG TAA CTG G and 5′ GAA GCC CTG AGA AGT TTA GAG TAA ATT GGG primers were used to amplify a 198 bp DNA fragment. PCR conditions involved initial denaturation at 95°C for 3 min followed by 35 cycles at 95°C for 20 sec, 65°C for 30 sec, and 72°C for 30 sec.

The PCR product was cut with three units of the AlwNI restriction enzyme at 37°C overnight; the uncut PCR product represented the G allele and the restriction fragments of 99 bp represented the T allele. The restriction fragments were separated on 10% polyacrylamide gel. All of the chemicals used were produced by Fermentas (Burlington, Canada).

A total of 13 variables were evaluated: age, length of hospital stay, duration of fever, height, height-for-age percentile, weight, weight-for-age percentile, weight-for-height percentile, *FTO* polymorphisms, clinical condition (fever, SIRS, sepsis, severe sepsis, septic shock, MODS), pathogen type, sex, and survival/death.

STATISTICAL ANALYSIS

Normal distribution of data samples was verified using the Anderson–Darling test. One-way analysis of variance (ANOVA) was used to compare mean values of data samples created with categorical variables (*FTO* genotype and clinical condition). In cases where data did not meet the statistical assumptions indicated by ANOVA (normality, homogeneity of variances), the non-parametric Kruskal–Wallis test was used. The two data samples were compared in detail using the non-parametric Wilcoxon rank test or Student's *t*-test.

Frequencies in the contingency tables were compared using the chi-square test and, in the case of low frequencies, Fisher's exact test. Significance was set at a p value of 0.05 (0.10 for trend). For more information on the statistical methods used, refer to Agresti [23]. For statistical computing and graphics, we used R software version 3.3.1 (https://www.r-project.org/) and RStudio version 1.1.383 (https://www.rstudio.org/).

Descriptive statistics were used for the basic characterization of subjects. Following previous protocols [14,15], individual genotypes were distinguished and labelled as follows: the risky homozygote (TT) associated with lower weight, the heterozygote (TG), and the potentially protective homozygote (GG). We conducted a statistical evaluation of all variables. For a more reliable assessment of the data sets, we collapsed the protective genotypes (carriers of the G allele) together. First, we evaluated the influence of the *FTO* polymorphism on weight-associated anthropometric parameters. Second, we compared the occurrence of *FTO* variants between the FS and SC groups. Third, we analyzed the occurrence of *FTO* variants across the different age subgroups.

RESULTS

Most of the patients (68.1%) were admitted to the ICU due to infection. The remaining 30.9% were admitted due to trauma or another surgical condition. Overall survival was 95.8% out of the 598 patients enrolled. All patients who underwent a febrile episode, SIRS, or sepsis survived. The mortality rate was 5.6% (4 out of 71 patients) in the severe sepsis subgroup, and 56.8% (21 out of 37 patients) in the septic shock and MODS subgroup. In the remaining 9 patients, the severity of sepsis could not be determined. Detailed characteristics of the subjects are given in Table 1.

We observed no significant differences in weight between genotypes in patients overall, as indicated by ANOVA. However, when comparing TT homozygotes with G-allele carriers, we observed a marginally higher average weight ($p = 0.22$) in carriers of at least one G allele. Pair-wise comparisons between TT homozygotes and G-allele carriers revealed a significant difference for the weight-age percentile ($p = 0.04$).

Age-dependent analysis of the association between *FTO* genotype and body weight revealed a significant effect, mostly in the highest age category of 15 to 18 years, as indicated by the non-parametric Kruskal–Wallis test ($p = 0.04$). We observed a similar effect on the weight-for-age percentile ($p = 0.02$). There were borderline non-significant differences in weight-for-height percentiles for the individual *FTO* variants, as indicated by both the non-parametric Kruskal–Wallis test ($p = 0.06$) and ANOVA ($p = 0.06$). In the 15–18 age group, duration of fever was significantly lower in G-allele carriers, as indicated by the Wilcoxon signed-rank test ($p = 0.002$). We observed no significant difference in the dependence between the *FTO* polymorphism and the duration of hospitalization ($p = 0.07$).

Similarly, there was no significant difference in the frequency of *FTO* genotypes between the entire group of patients and the population. However, we noted a significant difference ($p = 0.03$) for *FTO* genotypes in the FS group compared to the SC group (27.5% vs. 39.3% of TT homozygotes). The difference was even more pronounced when comparing TT homozygotes with G-allele carriers ($p = 0.007$, OR = 0.59, 95% CI = 0.39–0.87). The absolute and relative frequencies of *FTO* genotypes within both groups are shown in Table 2.

After collapsing G-allele carriers and TT homozygotes together, we identified a difference between the control group and the SC group, albeit at a 10% significance level ($p = 0.09$, OR = 0.81, 95% CI = 0.62–1.06). There was no significant difference in the frequency of *FTO* genotypes between survivors and non-survivors.

Table 1

Clinical characteristics of examined patients

	N	
Total number of patients	598	
Boys/Girls	325/273	
		Survival rate (%)
Overall survival	573	95.8
Severity of condition		
Febrile	130	100
SIRS	314	100
Sepsis	37	100
Severe sepsis	71	94
Septic shock and MODS	37	43
Confirmed infection at ICU	297	
Cause of infection	N (%)	
Gram-positive bacteria	123 (41)	
Gram-negative bacteria	112 (38)	
Viruses	37 (13)	
Fungi or other infectious agents	27 (8)	
Site of infection		
Respiratory	184 (31)	
Urogenital	60 (10)	
Central nervous system	72 (12)	
Abdominal infection	55 (9)	
Other infection	43 (7)	
Trauma or other surgical condition	180 (31)	

Table 2

Absolute and relative frequencies of *FTO* genotypes

Group	GG	TG	TT	Comparison with control group
	N (%)	N (%)	N (%)	
Control group	112 (18)	308 (50)	196 (32)	NA
Patient group	103 (17)	315 (53)	180 (30)	0.65
FS	81 (18)	241 (54)	122 (28)	0.28
SC	22 (15)	66 (45)	57 (39)	0.22*****
Age range				
0–3 years	31 (18)	86 (51)	53 (31)	0.99
3–6 years	18 (19)	43 (45)	34 (36)	0.67
6–9 years	13 (20)	38 (58)	15 (23)	0.31
9–12 years	6 (11)	32 (56)	19 (33)	0.34
12–15 years	17 (20)	39 (46)	29 (34)	0.77
15–18 years	17 (15)	70 (63)	25 (22)	**0.04**
18–19 years	1 (9)	5 (46)	5 (46)	0.99

* $p = 0.01$, OR = 0.59, and 95% CI = 0.39–0.87 for SC vs. FS.

FS = febrile patients and/or those with systemic inflammatory response syndrome (SIRS); SC = patients with one or more of the following severe conditions – sepsis, severe sepsis, septic shock, or multiple organ dysfunction syndrome (MODS).

DISCUSSION

Our results suggest that a common polymorphism within the *FTO* gene may, at least in paediatric patients, be linked to increased risk of sepsis. Alleles and genotypes associated with increased BMI seem to be protective against severe sepsis. The idea that susceptibility to infection and mortality might have a significant heritable component was first proposed decades ago by Sørensen *et al.* [24]. They reported an almost six-fold increase in infection-associated mortality in cases where at least one parent under the age of 50 had died of infection.

Numerous studies have focused on the potential association between different polymorphisms, mostly SNPs, and increased risk of severe sepsis [25]. In addition, several genome-wide association studies [10,26] have reported significant associations with various infection outcomes. Unfortunately, given the wide range of patient types and outcomes analyzed, the results of these studies cannot be universally applied.

To our knowledge, our study is the first to investigate the link between an *FTO* polymorphism and sepsis in humans. Although the connection between sepsis and *FTO* has not been documented in previous genome-wide association studies, it seems a plausible candidate. For example, *FTO* is a major genetic determinant of body weight [15] and, despite inconclusive results, overweight is understood to protect against the severity of sepsis and sepsis-associated mortality [12,13]. Moreover, *FTO* variants have been associated with increased risk of tuberculosis [27] and increased susceptibility to Gram-positive bacterial infections [28].

Recent experimental and clinical studies have confirmed the role of *FTO* in the pathogenesis of sepsis. Mice treated with entacapone, a specific inhibitor of *FTO* activity, exhibited significantly lower mortality than control animals following treatment with lipopolysaccharides. In human subjects, monocyte expression of *FTO* was found to be significantly lower in patients with sepsis compared to healthy volunteers. The authors hypothesized that higher *FTO* expression, which initially promotes the development of sepsis, may become inhibited at a later stage due to the feedback effect [29]. Similarly, *FTO* has been shown to be downregulated in animals with LPS-induced myocardial injury [30] and by rat cardiomyoblasts after LPS administration [31]. One study found that in patients with sepsis-associated encephalopathy, expression of *FTO* was significantly downregulated compared to controls [32]. Finally, mRNA sequencing analysis revealed lower expression of *FTO* in sepsis patients than in control subjects [33,34]

Importantly, it has been suggested that epigenetic mechanisms may make subjects more prone to sepsis generally or even to greater severity of sepsis [35] and *FTO* has been recognized as an important epigenetic mediator [16].

Various studies have demonstrated both the pleiotropy of genetic variants within the *FTO* gene as well as the effects of first-intron *FTO* polymorphisms. It has been confirmed that these polymorphisms play roles in determining BMI values. Notably, identical polymorphisms have been independently associated with, for example, type 2 diabetes [36] and its complications [37], some types of cancer [38], renal failure [39], and even total mortality [40].

Our study extends the range of diseases associated with *FTO* polymorphisms to include sepsis. We found that the risk of severe sepsis was lower in carriers of at least one obesity-associated allele (rs17817449-G). Additionally, we identified the same trend (reflected in p values ranging from 0.05 to 0.1) between the general population and the group of patients as a whole. The fact, that adults, and not children were used for comparison seems not to be of importance, as there has not been described some trend in genotypes between different age groups with exception of very old subjects [40].

Nonetheless, our study is not without its limitations. Firstly, we lack a confirmatory group of patients for validation. Secondly, there was a significant age difference between the groups and finally, we don't have information's about potential sepsis history in our control group of subjects.

Regrettably, despite our study being one of the largest paediatrics performed thus far, we were unable to draw any definitive conclusion regarding the potential effect of *FTO* on sepsis mortality. Therefore, our results need to be confirmed in subsequent studies.

CONCLUSION

Our results indicate that a common polymorphism within the *FTO* gene, an epigenetic modifier, may be associated with sepsis, severe sepsis, septic shock, and MODS in children.

Introducere: Sepsisul este una dintre cele mai frecvente cauze de deces la pacienții internați în unitățile de terapie intensivă (UTI). Dezvoltarea sepsisului este influențată semnificativ de predispoziția genetică. În acest studiu, evidențiem o potențială asociere între o variantă a masei grase și a genei asociate obezității (FTO) și riscul de sepsis la copii și adolescenți.

Metode: Am investigat un polimorfism FTO a primului intron (rs17817449) prin compararea unui grup de afecțiuni severe (SC), care cuprinde 598 de copii și adolescenți (cu vârste între 0–19 ani) internați într-o secție de terapie intensivă cu febră, sindrom de răspuns inflamator sistemic (SIRS), sepsis, sepsis sever, șoc septic sau sindrom de disfuncție a mai multor organe (MODS), cu un grup martor format din 616 adulți tineri sănătoși.

Rezultate: Am observat o prevalență mai mică ($p < 0,01$; OR = 0,59, 95% CI = 0,39–0,87) a genotipului FTO TT la pacienții febrili și SIRS comparativ cu pacienții cu boală severă. A existat o tendință limită către o prevalență mai scăzută a genotipului FTO TT în grupul de control comparativ cu grupul SC ($p < 0,09$, OR = 0,81, 95% CI = 0,62–1,06).

Concluzii: Descoperirile noastre sugerează că rs17817449, un polimorfism FTO obișnuit, poate fi un predictor al sepsisului la pacienții pediatrici și că greutatea corporală mai mare protejează împotriva acestei complicații clinice.

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