

VISUOMENĖS SVEIKATA

Environmental risk factors in prediction of childhood prediabetes

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Key words: prediabetes; schoolchildren; environmental risk factors; islet cell autoantibodies; case-control study.

Summary. *Objective.* The damage of beta cells occurs during the asymptomatic prodromal period called prediabetes before onset of diabetes mellitus. It is characterized by the presence of islet cell autoantibodies (ICAs). The aim of this study was to find out what environmental factors predict ICA seroconversion in healthy schoolchildren in Lithuania.

Material and methods. Sera from 3053 nondiabetic schoolchildren living in Lithuania were investigated for ICAs. ICAs were measured in undiluted sera by indirect immunofluorescence method. All ICA-positive and randomly selected ICA-negative children were invited to participate in the study. Response rate in the families of ICA-positive children was 100% and in ICA-negative – 76.5%. Data from 13 ICA-positive and 199 ICA-negative schoolchildren were included in the analysis. Information on the environmental factors was collected via questionnaires.

Results. Proportions of breastfed children were similar in ICA-positive and ICA-negative schoolchildren. Full cow's milk was introduced at one month of age or earlier more often in ICA-positive than ICA-negative schoolchildren (8.3% and 1.1%, respectively; $P=0.05$). Cereal before 3 months of age was introduced more often in ICA-positive than ICA-negative schoolchildren (7.7% and 0.5%, respectively; $P=0.01$). The mothers of cases took medicine during pregnancy more often than mothers of controls did (61.5% and 14.1%, respectively; $P<0.001$). More than half (53.8%) of ICA-positive children lived in homes where family members were smoking indoors, while this was recorded only for 26.6% of controls ($P=0.04$).

Conclusions. Early introduction of cow's milk and cereal, the intake of medicine during pregnancy, and indoor smoking of family members are risk factors that predict the development of prediabetes among Lithuanian children.

Introduction

Type 1 diabetes mellitus is an autoimmune disease caused by the selective destruction of the insulin-producing pancreatic beta cells (1). This was understood when islet cell autoantibodies (ICAs) were first found in sera of patients with type 1 diabetes mellitus (2). Later, autoantibodies to glutamic acid decarboxylase (GAD), protein tyrosine phosphatase-like molecule (IA-2), and insulin autoantibodies (IAA) were identified (3, 4).

ICAs usually occur before the onset of type 1 diabetes mellitus (5). These autoantibodies are markers of the ongoing beta cell damage during the asymptomatic

prodromal period called prediabetes or preclinical diabetes (6). The detection of autoantibodies has been associated with increased risk of type 1 diabetes mellitus, especially in first-degree relatives (7), schoolchildren (8), and very young children (9). Some of authors have discovered that detection of ICAs has higher sensitivity compared to other autoantibodies related to diabetes (10).

The prevalence of preclinical diabetes (positivity for ICAs) among healthy schoolchildren and first-degree relatives is higher than the expected prevalence of overt diabetes, suggesting that some subjects with prediabetes will never develop clinically overt diabetes

mellitus (11).

Onset of type 1 diabetes mellitus is determined by genetic predisposition and environmental factors. The environmental risk factors generally found are the following: the short duration of breastfeeding, the early introduction of cow's milk and other food such as cereal, eggs, meat, vitamins A and D (12–14). Other factors may also play a role, such as low level of maternal education (15) and the place of living (16). The studies have shown that maternal age, pregnancy period, neonatal illness (13, 17), and vaccination (18) may play a role. The immune process in pancreas can also be triggered by infections (18) and stressful events in life (19, 20).

The aim of this study was to analyze whether risk factors related to type 1 diabetes mellitus (21) also influence the development of childhood prediabetes in Lithuanian children.

Material and methods

Sera from 3053 (1449 boys and 1604 girls) non-diabetic schoolchildren living in Kaunas region of Lithuania were collected under nonfasting conditions during 1994 to 1998 (22). The median age of children was 11.7 years, ranging from 5.5 to 15 years. ICAs were measured in undiluted sera by indirect immunofluorescence (7). End-point titres of samples were converted to the units of Juvenile Diabetes Foundation (JDF) by comparison with a standard curve of $\log_2$ JDF units compared with $\log_2$ of end-point titre of standard sera. The threshold of detection was 4 JDF units. The assay achieved a sensitivity of 81% with a specificity of 86% in the First IDS Combined Antibody Workshop (23). All ICA-positive and randomly selected ICA-negative children were invited to participate in the study. Response rate in ICA-positive children families was 100% and in ICA-negative 76.5%. Data from 13 (6 boys and 7 girls) ICA-positive and 199 (95 boys and 104 girls) ICA-negative schoolchildren were included in the analysis during 1998 to 1999. The mean ages of ICA-positive and ICA-negative schoolchildren were 15.6 ± 2.1 years and 15.3 ± 2.2 years, respectively. All children and their parents were asked to fill in questionnaires. There were questions about nutrition in babyhood: duration of exclusive and total breastfeeding, time of introduction of cow's milk substitutes (including baby formula, c-milk), full cow's milk, cereal, meat, eggs, soy products, and other solid foods, vitamin D. C-milk is homemade baby food, which is based on cereal-water mixed in proportion 2:1 with cow's milk. Questions regarding pregnancy period, maternal age, neonatal period, and first

year of life and information regarding social factors were included as well (questions about living conditions and place of living, mother's education, occupation, employment, child's attendance of kindergarten at any time before school). Information about infections throughout the life, vaccination was involved too. The questionnaire has been described previously (14, 24).

The study was approved by the Research Ethics Committee of Kaunas University of Medicine, Lithuania.

Statistical analysis. Comparison of means between groups of cases and controls was performed by the Student *t* test. Proportions were compared using chi-square test. Differences were considered significant at $P < 0.05$. For the proportions, 95% confidence intervals (CI) were calculated. Statistical package SPSS 10.0 for Windows release was used for the data analysis.

Results

The percentages of breastfed children were similar in ICA-positive and ICA-negative schoolchildren (92.3% and 89.9%, respectively; $P = 0.78$).

The mean duration of exclusive breastfeeding was the same for both groups: 2.4 ± 1.5 months for ICA-positive and 2.5 ± 2.0 months for ICA-negative schoolchildren ($P = 0.82$). We observed that similar percentages of children in both groups were exclusively breastfed. The prevalence of exclusive breastfeeding up to the age of 12 months is presented in Fig. 1.

The mean duration of total breastfeeding was similar for ICA-positive (5.0 ± 4.1 months) and ICA-negative children (4.2 ± 3.5 months, $P = 0.45$). We observed that ICA-negative children tended to be more frequently breastfed during the first 3 months than ICA-positive children (Fig. 2). However, 33.3% (4/12) of ICA-positive and only 14% (25/179) of ICA-negative schoolchildren were breastfed for 8 months or longer ($P = 0.07$). The prevalence of total breastfeeding up to the age of 12 months is presented in Fig. 2.

Cow's milk substitutes were introduced at the same time in ICA-positive and ICA-negative children (2.7 ± 1.9 and 2.74 ± 1.9 months, respectively; $P = 0.94$). The mean age at the introduction of full cow's milk was the same in both groups (4.9 months). However, full cow's milk was introduced at the age of 1 month or earlier more often in ICA-positive than ICA-negative schoolchildren (8.3% and 1.1%, respectively, $P = 0.05$).

Cereal was introduced before 3 months of age more frequently in ICA-positive than ICA-negative schoolchildren (7.7% and 0.5%, respectively, $P = 0.01$). Eggs,

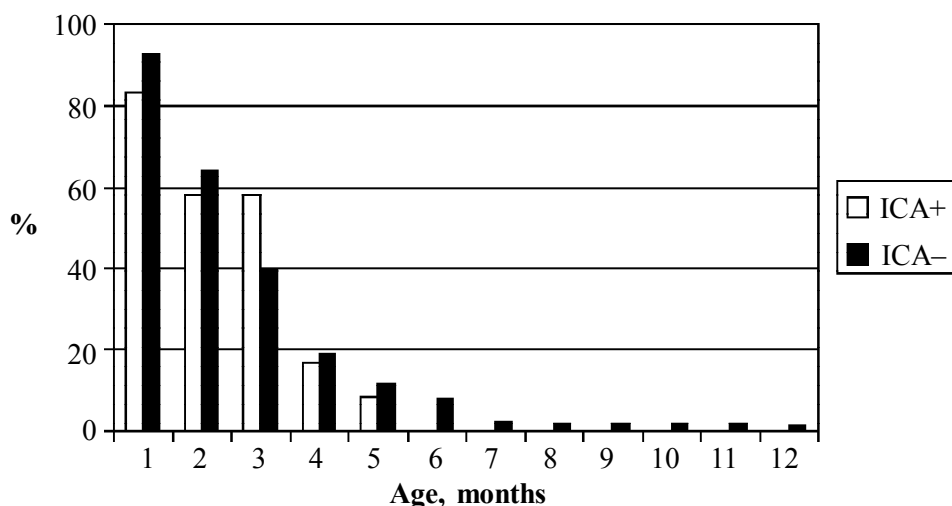


Fig. 1. The prevalence of exclusive breastfeeding up to the age of 12 months in ICA-positive (ICA+) and ICA-negative (ICA-) schoolchildren

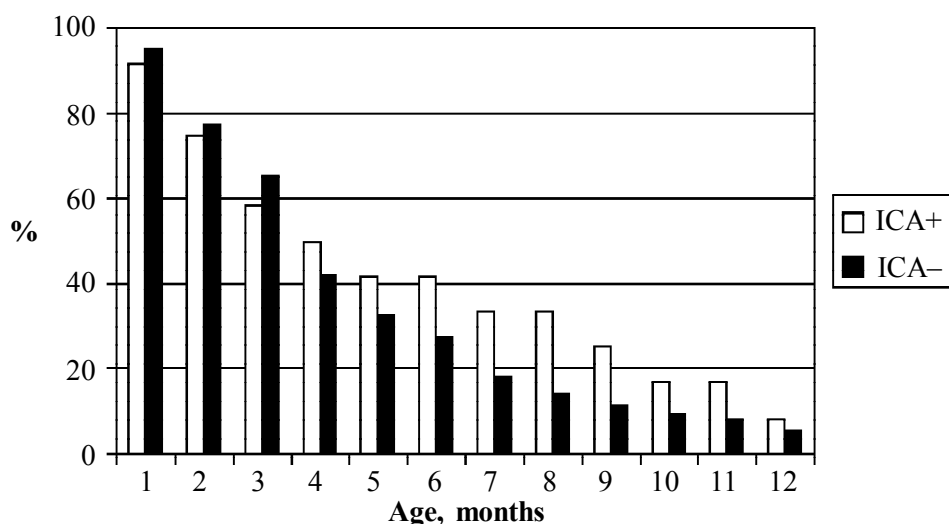


Fig. 2. The prevalence of total breastfeeding up to the age of 12 months in ICA-positive (ICA+) and ICA-negative (ICA-) schoolchildren

meat, vitamin D were introduced at similar ages in both groups (Table 1).

Allergy to cow's milk occurred significantly more often among ICA-positive than ICA-negative children (23.1% and 7.5%, respectively, $P=0.05$). Other problems as diarrhea, rash at the time of introduction of various other foods were reported rarely and similarly by cases and controls.

The mean maternal age at delivery was the same for mothers of ICA-positive (26.2 ± 4.6 years) and ICA-negative children (26.4 ± 5.1 years, $P=0.94$). However, slightly more mothers aged 30 years and older at the time of delivery were found for ICA-positive children compared with ICA-negative ones (23.1% and 17.6%, respectively; $P=0.62$).

Infections during pregnancy were recorded nearly twice more often for mothers of ICA-positive children compared with ICA-negative ones (38.5% and 20.6%, respectively; $P=0.13$). The mothers of cases took medicine more often during pregnancy (61.5% and 14.1%, respectively; $P<0.001$).

Toxicosis during pregnancy (preeclampsia) was observed slightly more often in mothers of ICA-positive compared with mothers of ICA-negative children (23.1% and 15.1%, respectively; $P=0.44$).

The proportion of premature newborns was two times higher in ICA-positive schoolchildren compared with ICA-negative ones (7.7% and 3.5%, respectively; $P=0.44$).

Icterus in neonatal period was recorded somewhat

Table 1. Frequencies and odds ratio (OR) of introduction of food during the first year of age among ICA-positive (ICA+) and ICA-negative (ICA-) schoolchildren

Age at the time of food introduction (in months)	ICA+ n (%)	ICA- n (%)	OR (95% CI)	P
Cow's milk substitutions ≤3 >3	6 (60.0) 4 (40.0)	113 (69.3) 50 (30.7)	1.51 (0.41–5.57)	0.54
Full cow's milk ≤1 >1	1 (8.3) 11 (91.7)	2 (1.1) 178 (98.9)	0.12 (0.01–1.47)	0.05
Full cow's milk ≤3 >3	3 (25.0) 9 (75.0)	29 (16.1) 151 (83.9)	0.58 (0.15–2.26)	0.42
Food with soy ≤3 >3	1 (100) 0	4 (16.0) 21 (84.0)	–	0.04
Cereal <3 ≥3	1 (7.7) 12 (92.3)	1 (0.5) 188 (99.5)	0.06 (0.004–1.08)	0.01
Eggs <5 ≥5	6 (46.2) 7 (53.8)	60 (31.9) 128 (68.1)	0.55 (0.18–1.70)	0.29
Meat <8 ≥8	11 (84.6) 2 (15.4)	153 (79.3) 40 (20.7)	0.70 (0.15–3.27)	0.644
Vitamin D <2 ≥2	3 (33.3) 6 (66.7)	46 (38.0) 75 (62.0)	1.23 (0.29–5.15)	0.78

CI – confidence interval.

more often in cases than controls (23.1% and 17.1%, respectively; $P=0.58$). ICA-positive children with icterus were treated with phototherapy significantly more often (33% and 0%, respectively; $P=0.001$) than ICA-negative, and blood transfusions were given more often (33.3% and 5.9%, respectively; $P=0.095$).

More mothers of ICA-positive children tended to have low level of education (secondary or less than secondary) than mothers of control children did (38.5% and 22.1%, respectively; $P=0.18$).

Mothers of cases tended to live in rural area during pregnancy than mothers of controls (15.4% and 11.1%, respectively; $P=0.63$). Later, during the first year of child's life, 11.6% of controls' families compared with no families of cases lived in rural area ($P=0.19$).

More than half (53.8%) of ICA-positive children lived at homes where family members were smoking indoors while this was recorded only in 26.6% of controls ($P=0.04$).

More than three-fourths (84.6%) of ICA-positive

and 68.7% of ICA-negative children attended kindergarten for at least 3 months ($P=0.23$).

More than two-thirds (69.2%) of ICA-positive children were vaccinated according to vaccination calendar as compared to 83.9% of controls ($P=0.17$). Frequencies of vaccination and infections are presented in Tables 2 and 3. No significant differences were observed between groups analyzing frequency of separate infectious diseases and different vaccinations.

Infections during the last 6-month period before the study were recorded almost two-fold more frequently for ICA-negative schoolchildren compared with ICA-positive schoolchildren (15.1% and 7.7%, respectively; $P=0.47$).

The frequency of such factors as mother's smoking during pregnancy period, child's birth weight, treatment at hospital during the first month of life, sensitivity to infections, serious events during the last 6-month period until the study did not differ between cases and controls.

Table 2. Frequencies of vaccination among ICA-positive (ICA+) and ICA-negative (ICA-) schoolchildren

Vaccine	ICA+ vaccinated, n / total ICA+, n %	ICA- vaccinated, n / total ICA-, n %	P
BCG	13/13 100	190/199 95.5	0.43
Polio vaccine	13/13 100	186/199 93.5	0.34
DTaP	13/13 100	187/199 94.0	0.36
Rubella vaccine	8/13 61.5	110/199 55.3	0.66
Measles	13/13 100	185/199 93.0	0.32
Mumps	6/13 46.2	90/199 45.2	0.95

BCG – bacille Calmette-Guérin vaccine; DTaP – diphtheria-tetanus-acellular pertussis vaccine.

Table 3. Frequencies of infections in ICA-positive (ICA+) and ICA-negative (ICA-) schoolchildren

Infectious disease	ICA+ with infection, n / total ICA+, n %	ICA- with infection, n / total ICA-, n %	P
Varicella	12/13 92.3	148/199 74.4	0.15
Measles	0/13 0	24/199 12.1	0.18
Rubella	3/13 23.1	54/199 27.4	0.73
Mumps	2/13 15.4	40/199 20.1	0.68
Pertussis	0/13 0	12/199 6.0	0.36

Discussion

The aim of this study was to analyze the environmental factors that predict ICA seroconversion (pre-diabetes) in healthy schoolchildren.

The weakness of this study is the small sample size. This may explain that several of observed differences do not become statistically significant although the differences in figures are great. We have therefore chosen to present differences as such, even though just a few are statistically significant. Furthermore, data were collected retrospectively. Recall bias might exist among parents, but as nobody knew who had ICA or not, such bias should not have obscured our results.

The short duration of breastfeeding especially less than 3 months is a well-known risk factor for type 1 diabetes mellitus (14). Our data have showed that the duration of breastfeeding did not have any impact on the development of prediabetes. More ICA-positive children were breastfed for 8 months and longer as compared to ICA-negative ones, while exclusive breastfeeding during the first months showed to be protective against development of ICAs.

Early introduction of cow's milk substitutes and full cow's milk can increase the risk of type 1 diabetes mellitus (12). Some recent studies have confirmed associations between the early introduction of cow's

milk and development of diabetes (14, 25). Studies in some countries have shown that high consumption of cow's milk increased the risk of type 1 diabetes mellitus too (25, 26). In the present study, full cow's milk was introduced before the second month more often in ICA-positive schoolchildren than ICA-negative ones.

However, ICA-positive children had allergy to cow's milk significantly more often than ICA-negative children, which, in fact, results in lower consumption of cow's milk later.

The last studies with rats showed that food (wheat, soy) proteins are important as a risk factor for 1 type diabetes mellitus too (27). These proteins, particularly cow's milk proteins, may activate autoimmune process in pancreas. Our data have shown that cereal and soy were introduced before 3 months of age more frequently in ICA-positive schoolchildren than ICA-negative schoolchildren ($P=0.01$ and $P=0.04$, respectively).

The pathogenic process of autoimmune β -cell destruction may be initiated in utero or around the time of delivery when developing fetus and neonates are particularly vulnerable with their immune system remaining immature (13, 28). Maternal infections during pregnancy period (13, 29), preeclampsia (13, 17), blood group incompatibility (17, 30, 31), neonatal illness (13, 14), and common infections (32) are factors that might trigger autoimmune β -cell destruction. Our data show that mothers of ICA-positive children took medicine significantly more often during pregnancy. They took penicillin, calcium gluconate, antihypertensive drugs, and metoclopramide. Infections may initiate an immune process in pancreas. Icterus in neonatal period was recorded more frequently among cases in our study. Icterus might be as the expression of maternal and fetal blood group incompatibility. The children with icterus were treated with phototherapy and blood transfusions significantly more often. The mechanism triggering autoimmune destruction is unknown; however, that treatment could initiate the slowly progressing autoimmune process and later β -cell destruction and prediabetes (17, 31). On the other hand, there are a number of possibilities

that some risk genes in HLA system contribute to both type 1 diabetes mellitus and blood group incompatibility, or one event might be a cause of the following one, like blood group incompatibility might cause immune disturbance in early childhood that leads to the type 1 diabetes mellitus later in life (30).

We have obtained very interesting data on smoking. The family members of 58.3% of ICA-positive children were smoking indoors compared to only 26.6% of family members of ICA-negative children. Indoor and outdoor smoking, tobacco smoke exposure, and its impact on children's health has been investigated in Sweden (33, 34). Our data need further studies.

Infections caused by viruses as the risk factor of type 1 diabetes mellitus are mentioned in various studies. We found no differences in the prevalence of specific infections between the two groups. However, infections during the last 6 months before study more frequently occurred among ICA-negative children. If anything, our findings suggested that recent infections might decrease prediabetes risk. Vaccination can protect against diabetes (18, 35) or increase the risk of diabetes (36). Some studies found no evidence that any common childhood vaccination modified the risk of diabetes (37). We found that vaccination according to vaccination calendar had no impact on the development of prediabetes.

Conclusions

Certain environmental factors have earlier been identified as risk factors for development of diabetes mellitus, and we can confirm that some of these factors increase the risk of developing ICAs among Lithuanian children. Early introduction of cow's milk and cereal, intake of medicine during pregnancy, and indoor smoking of family members are risk factors. These results must be interpreted with caution; however, there is a need for confirmation in larger data set.

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Aplinkos rizikos veiksniai, sukeliantys vaikų ikidibetinę būklę

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Raktažodžiai: ikidibetinė būklė, moksleiviai, aplinkos rizikos veiksniai, antikūnai prieš kasos ląsteles, atvejo ir kontrolės tyrimas.

Santrauka. *Išvadas.* Įžanginis diabeto periodas, kai atsiranda pirmieji kasos beta ląstelių pažeidimai, vadinamas ikidiabetine būkle. Tuo metu kraujyje jau randami antikūnai prieš kasos beta ląsteles. Tyrimo tikslas – nustatyti, kurie aplinkos veiksniai lemia antikūnų prieš kasos beta ląsteles atsiradimą sveikiems Lietuvos moksleiviams.

Tyrimo medžiaga ir metodai. 3035 sveikiems Lietuvos moksleiviams buvo tirti antikūnai prieš kasos beta ląsteles. Antikūnams nustatyti naudotas netiesioginis imunofluorescencinis metodas. Dalyvauti tyrime buvo pakviesti visi moksleiviai, kuriems rasta antikūnų, ir atsitiktinai atrinkti moksleiviai, kuriems nerasta antikūnų prieš kasos beta ląsteles. Dalyvauti tyrime sutiko 13 moksleivių, kuriems rasta antikūnų, ir 199 moksleivių, kuriems antikūnų nerasta, atsako dažnumas 100 ir 76,5 proc., atitinkamai. Informacija apie aplinkos rizikos veiksnius surinkta pildant klausimynus.

Rezultatai. Motinos pienu buvo maitintas vienodas skaičius vaikų, kuriems rasta ir nerasta antikūnų prieš kasos beta ląsteles. Moksleiviai, kuriems rasta antikūnų prieš kasos beta ląsteles, buvo pradėti maitinti karvės pienu vieno mėnesio amžiaus ar anksčiau, dažniau nei kontrolinės grupės moksleiviai (atitinkamai – 8,3 ir 1,1 proc., $p=0,05$). Kruopų košė pradėta duoti iki trijų mėnesių amžiaus dažniau vaikams, kuriems rasta antikūnų prieš kasos beta ląsteles nei kontrolinės grupės vaikams (atitinkamai – 7,7 ir 0,5 proc., $p=0,01$). Vaikų, kuriems rasta antikūnų prieš kasos beta ląsteles, motinos nėštumo metu dažniau vartojo vaistus nei motinos vaikų, kuriems antikūnų nerasta (atitinkamai – 61,5 ir 14,1 proc., $p<0,001$). 53,8 proc. moksleivių, kuriems rasta antikūnų prieš kasos beta ląsteles, šeimos nariai rūko namuose, o kontrolinės grupės moksleivių – tik 26,6 proc., $p=0,04$.

Išvados. Anksti pradėtas vaikams duoti karvės pienas, kruopų košė, nėščiosios vaistų vartojimas bei šeimos narių rūkymas namuose priklauso rizikos veiksniams, kurie gali turėti įtakos vaikų ikidiabetinės būklės pasireiškimui.

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