TEDDY–The Environmental Determinants of Diabetes in the Young

An Observational Clinical Trial

WILLIAM A. HAGOPIAN,[a] ÅKE LERNMARK,[b] MARIAN J. REWERS,[c] OLLI G. SIMELL,[d] JIN-XIONG SHE,[e] ANETTE G. ZIEGLER,[f] JEFFREY P. KRISCHER,[g] AND BEENA AKOLKAR[h]

[a]*Pacific Northwest Research Institute, Seattle, Washington 98122, USA*

[b]*University Hospital MAS, 20522 Malmö, Sweden*

[c]*University of Colorado, Denver, Colorado 80162, USA*

[d]*Turku University Central Hospital, Turku, 20520 Finland, USA*

[e]*Medical College of Georgia, Augusta, Georgia 30912, USA*

[f]*Diabetes Research Institute, 80804 Munich, Germany*

[g]*University of South Florida, Tampa, Florida 33612, USA*

[h]*National Institutes of Health, Bethesda, Maryland 20892, USA*

ABSTRACT: The aim of the TEDDY study is to identify infectious agents, dietary factors, or other environmental agents, including psychosocial factors, which may either trigger islet autoimmunity, type 1 diabetes mellitus (T1DM), or both. The study has two end points: (*a*) appearance of islet autoantibodies and (*b*) clinical diagnosis of T1DM. Six clinical centers screen newborns for high-risk HLA genotypes. As of December 2005 a total of 54,470 newborns have been screened. High-risk HLA genotypes among 53,560 general population (GP) infants were 2576 (4.8%) and among 910 newborns with a first-degree relative (FDR) were 194 (21%). A total of 1061 children have been enrolled. The initial enrollment results demonstrate the feasibility of this complex and demanding a prospective study.

KEYWORDS: type 1 diabetes; islet autoantibodies; HLA; virus

INTRODUCTION

The incidence of type 1 diabetes mellitus (T1DM), one of the most common and serious chronic diseases in children is increasing worldwide.[1,2] While

Address for correspondence: Åke Lernmark, Ph.D., CRC Lund University, Department of Clinical Sciences, University Hospital MAS, SE-205 02 Malmö, Sweden. Voice: +46 40 391901; fax: +46 40 39 19 19.
e-mail: Ake.lernmark@med.lu.se

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the incidence is highest in Scandinavia (30–50/100,000), intermediate in the United States (15–25/100,000 in 1998), and somewhat lower in Central and Eastern Europe (5–15/100,000), it is unclear to what extent these geographic differences may reflect variation in genetic susceptibility, in prevalence of causal environmental factors, or both; although major advances have been made in the identification of genetic factors that confer susceptibility or resistance to T1DM.[3,4] The dissection of the etiology of T1DM is further complicated by epidemiological observations that approximately 85–90% of new onset patients have no first degree relative (FDR) with T1DM despite a strong familiar clustering of patients.[5] Genetic variability in the HLA region explains ~50% of the familiar clustering[6] but other genes identified so far provide more modest contributions to risk.[3,4] Additional factors are important, because only 1 out of 15 people in the general population (GP) with the highest risk HLA genotypes develops T1DM.

The mechanisms by which environmental factors may trigger either islet autoimmunity, T1DM, or both in susceptible subjects are not understood. The aim of the present multicenter study is to examine from birth high-risk GP children and FDR and systematically screen them for candidate environmental and genetic factors. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay, or reverse T1DM.

SUBJECTS AND METHODS

Subjects

A cohort of children with elevated genetic risk for T1DM is established by screening newborns from the GP and from families with FDR diagnosed with T1DM. A total of six clinical centers from Seattle, WA, Denver, CO, Augusta, GE, Munich, Germany, Turku, Finland, and Malmö, Sweden participate.

HLA Typing and Genetic Risk

Genetically susceptible children are identified through newborn HLA-DR/DQ screening. Genotype screening is performed using either a dried blood spot (DBS) punch or a small volume whole blood lysate (WBL) specimen. A screening blood sample is obtained either at birth as a cord blood sample or using heel stick capillary sample up to the age of 3 months. This exception is made to maximize the number of newborn relatives participating in this study. After polymerase chain reaction (PCR) amplification of exon 2 of the HLA Class II gene (DRB1, DQA1 or DQB1), alleles will be identified either by direct sequencing, oligonucleotide probe hybridization, or other genotyping techniques (TABLE 1).

TABLE 1. HLA genotypes used to enroll newborns in the TEDDY study

TEDDY genotype
DR4- DQA1*0301-DQB1*0302@ / DR3- DQA1*0501-DQB1*0201
DR4- DQA1*0301-DQB1*0302 / DR4- DQA1*0301-DQB1*0302
DR4- DQA1*0301-DQB1*0302@ / DR8- DQA1*0401-DQB1*0402
DR3-DQA1*0501-DQB1*0201 / DR3-DQA1*0501-DQB1*0201
DR4- DQA1*0301-DQB1*0302@ / DR4- DQA1*0301-DQB1*0201
DR4- DQA1*0301-DQB1*0302@ / DR1#- DQA1*0101-DQB1*0501
DR4- DQA1*0301-DQB1*0302@ /DR13-DQA1*0102-DQB1*0604
DR4- DQA1*0301-DQB1*0302 / DR4- DQA1*0301-DQB1*0304
DR4- DQA1*0301-DQB1*0302@ / DR9- DQA1*0301-DQB1*0303
DR3- DQA1*0501-DQB1*0201 / DR9- DQA1*0301-DQB1*0303

Genotypes a–d are eligible from the GP and genotypes a–j for FDR.
@Acceptable alleles in this haplotype include both DQB1*0302 and *0304.
#In this DQB1*0501 haplotype, DR10 must be excluded. Only DR1 is eligible.

Follow-Up Schedule for Children with Increased Genetic Risk

Children with increased genetic risk are followed for environmental exposures and diet with a clinic visit every 3 months for the first 4 years of life and then biannually until age the 15 years. Stool samples are collected to assess viral exposures at monthly intervals for the first 4 years of life and then biannually until the age 15. In addition, dietary, infectious, and psychosocial assessments are completed at each visit to the clinic.

RESULTS

The TEDDY study was initiated September 1, 2004 with the aim to screen 220,800 newborn children over a total of 4 years. After an initial start-up phase all six clinical centers have been recruiting newborns for about 1 year. As of December 2005 the data show that a total of 54,470 (98% of expected) newborns have been screened. High-risk HLA genotypes among 53,560 GP infants were 2576 (4.8%) and among 910 FDR newborns were 194 (21%). The HLA distribution of these children demonstrate that the 97% of the 2528 eligible children typed so far represents the high-risk genotypes a, b, c, and d (TABLE 2). A total of 1061 children have been enrolled at the end of December 2005. The first group of children has been followed for 1 year and the prospective analysis has continued successfully with only a few families leaving the study. One TEDDY infant has developed T1DM at 8 months of age.

DISCUSSION

The present report represents about 1-year experience in screening newborn children to be enrolled in the TEDDY study. The target to screen 55,200

TABLE 2. HLA genotypes among eligible and enrolled newborns in the TEDDY study

TEDDY genotype	Eligible *n*	%	Enrolled *n*	%
a	977	38.4	403	41.8
b	503	19.7	186	19.2
c	444	17.4	157	16.2
d	555	21.8	188	19.5
e	2	0.1	2	0.2
f	40	1.6	18	1.8
g	7	0.3	3	0.3
h	3	0.1	3	0.3
i	4	0.2	2	0.2
j	8	0.3	2	0.2
Total	2,543		964	

newborn children per year to reach 220,800 children over a 4-year period was reached. Consistent with the observations that only 10–15% of newly diagnosed T1DM children have an FDR with the disease,[5] it is noted that 910 (1.7%) of 54,470 screened newborns belong to this group. This frequency is far from a true reflection of the prevalence rate of T1DM in participating GPs but rather reflects our planned effort to screen children born in families with a father, mother, or sibling with T1DM. The rationale for a focus on FDR is the well-known risk for a child to develop T1DM if the father, mother, or a sibling (in this order) is affected as compared to the GP. The average increase is three- to eightfold which means that a higher proportion of newborns in the FDR group will not only reach the first end point of islet autoantibody positivity but also the second end point of T1DM during 15 years of follow up.

The HLA genotypes selected as TEDDY inclusion criteria (TABLE 1) represent both genotypes that confer the highest risk in population-based studies[7,8] as well as in family studies.[8,9] The a, b, c, and d TEDDY genotypes are also the genotypes that predominate subjects with T1DM regardless of whether they represent the GP or FDR. It is noted that the two most critical haplotype for T1DM risk is the DR4-DQA1*0301-B1*0302 and the DR3-DQA1*0501-B1*0201 haplotypes. In particular, the DR4-DQA1*0301-B1*0302 haplotype predominates and is present in 8 out of 10 of the TEDDY genotypes. Only the "d" and "j" haplotypes are non-DR4-DQA1*0301-B1*0302 and after 1 year of screening 20% of eligible children were DR3-DQA1*0501-B1*0201 homozygous. This group will serve as an important immunogenetics reference group with respect to trigger exposures and the development of islet autoantibodies.

The TEDDY study will provide an important opportunity to improve our understanding of the events leading to T1DM by studying from birth high-risk GP children and FDR and by systematic screening of candidate environmental and genetic factors. In addition, samples collected by TEDDY will create a valuable resource for investigators proposing innovative hypotheses concerning candidate environmental and genetic factors.

The long-term goal of the TEDDY study is the identification of infectious agents, dietary factors, or other environmental agents, including psychosocial factors, which trigger beta cell autoimmunity, T1DM, or both, in genetically susceptible individuals or which protect against the disease. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay, or reverse T1DM.

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APPENDIX

The Teddy Study Group

Colorado Clinical Center: Marian Rewers, M.D., Ph.D., PI,[1,4,6,10,11] Katherine Barriga,[12] Judith Baxter,[9,12] Ann Deas, George Eisenbarth, M.D., Ph.D., Lisa Emery, Patricia Gesualdo,[2,12] Michelle Hoffman,[12] Jill Norris, Ph.D.,[2,12] Kathleen Waugh,[7,12] Stacey Weber. University of Colorado at Denver and Health Sciences Center, Barbara Davis Center for Childhood Diabetes.

Georgia/Florida Clinical Center: Jin-Xiong She, Ph.D., PI,[1,3,4,11] Andy Muir, M.D.,[7] Desmond Schatz, M.D.,[*4,5,7,8] Diane Hopkins,[12] Leigh Steed,[12] Angela Choate,[*12] Katherine Silvis,[2] Meena Shankar,[*2] Yi-Hua Huang, Ph.D., Ping Yang, Wei-Peng Zheng, Hong-Jie Wang, Kim English and Richard McIndoe, Ph.D. Medical College of Georgia, *University of Florida.

Germany Clinical Center: Anette G. Ziegler, M.D., PI,[1,3,4,11] Ezio Bonifacio, Ph.D.,[*5] Andrea Baumgarten,[12] Sandra Hummel, Ph.D.,[2] Mathilde Kersting,[2] Stephanie Koenig,[2] Annette Knopff,[7] Angelika Locher,[12] Roswith Roth, Ph.D.,[9] Stefanie Schoen,[2] Petra Schwaiger,[7] Wolfgang Sichert-Hellert, Ph.D.,[2] Christiane Winkler,[2,12] Diana Zimmermann, Ph.D.[7,12] Diabetes Research Institute, *San Raffaele Institute.

Finland Clinical Center: Olli G. Simell, M.D., Ph.D., PI,[¥^1,4,11] Kirsti Nanto-Salonen, M.D., Ph.D.,[¥^12] Jorma Ilonen, M.D., Ph.D.,[¥3] Mikael Knip, M.D., Ph.D.,[*±] Riitta Veijola, M.D., Ph.D.,[µ¤] Tuula Simell, Ph.D.,[¥^9,12] Ulla Uusitalo, Ph.D.,[§2] Heikki Hyöty, M.D., Ph.D.,[*±6]

Suvi M. Virtanen, M.D., Ph.D.,[*§2] Carina Kronberg-Kippilä,[§2] Maija Torma,[¥^] Eeva Ruohonen,[¥^] Minna Romo,[¥^] Elina Mantymaki,[¥^] Tiina Niininen,[*±] Mia Nyblom,[*±] Aino Stenius.[µ¤] [¥]University of Turku, [*]University of Tampere, [µ]University of Oulu, [^]Turku University Hospital, [±]Tampere University Hospital, [¤]Oulu University Hospital, [§]National Public Health Institute, Finland.

Sweden Clinical Center: Åke Lernmark, Ph.D., PI,[1,3,4,5,8,10,11] Peter Almgren, Carin Andrén-Aronsson,[2] Eva Andersson, Sylvia Bianconi-Svensson,[2] Ulla-Marie Carlsson, Corrado Cilio, M.D., Ph.D., Joanna Gerardsson, Barbro Gustavsson, Anna Hansson,[2] Gertie Hansson,[12] Ida Hansson, Sten Ivarsson, M.D., Ph.D.,[6,7] Helena Larsson M.D., Elli Karlsson, Anastasia Katsarou M.D., Barbro Lernmark, Ph.D.,[9,12] Thea Massadakis, Anita Nilsson, Monica Sedig Järvirova, Birgitta Sjöberg, Anne Wallin, Åsa Wimar. Lund University.

Washington Clinical Center: William A. Hagopian, M.D., Ph.D., PI,[1,3,4,7,11] Michael Brantley,[7,12] Claire Cowen, Peng Hui, M.D., Ph.D., Kristen M. Hay,[2] Melissa Jackson, Viktoria Stepikova, Jennifer Ugale.[2,12] Pacific Northwest Research Institute.

Data Coordinating Center: Jeffrey P. Krischer, Ph.D., PI,[1,4,5,10,11] Carole Bray,[12] David Cuthbertson, Veena Gowda, Kimberly Hunt,[12] Shu Liu, Jamie Malloy, Cristina McCarthy,[12] Wendy McLeod,[2,9] Susan Moyers, Ph.D.,[2,10] Lavanya Nallamshetty, Susan Smith.[12] University of South Florida.

Project officer: Beena Akolkar, Ph.D.,[1,3,4,5,7,10,11] National Institutes of Diabetes and Digestive and Kidney Diseases.

Other contributors: Thomas Briese,[6] Columbia University, Henry Erlich,[3] Children's Hospital Oakland Research Institute, Suzanne Bennett Johnson,[9,12] Florida State University, Steve Oberste,[6] Centers for Disease Control and Prevention.

Committees:

[1]Ancillary Studies, [2]Diet, [3]Genetics [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Maternal Studies, [9]Psychosocial, [10]Quality Assurance, [11]Steering, [12]Study Coordinators.

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