Autoantibody order, timing predict genetically at-risk children most likely to get type 1 diabetes

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Children with multiple islet autoantibodies—biological markers of autoimmunity—are more likely to progress to symptomatic type 1 diabetes (T1D) than those who remain positive for a single autoantibody.

Now, new findings from The Environmental Determinants of Diabetes in the Young (TEDDY) study in the U.S. and Europe show that detailed information about the order, timing and type of autoantibodies appearing after the first autoantibody can significantly improve prediction of which children are most likely to progress to type 1 diabetes more rapidly.

The TEDDY analysis was published in the September 2020 issue of *Diabetes Care*.

"A better understanding of distinct autoantibody spreading is important, because it will allow us to identify at-risk children earlier in the disease process," said the study's lead author Kendra Vehik, Ph.D., a professor of epidemiology at the University of South Florida Health (USF Health) Morsani College of Medicine's Health Informatics Institute. "That means while children are still asymptomatic, we can start to look at interventions and strategies that may reduce, delay or stop the progression of type 1 diabetes."

While antibodies are molecules produced by the body's immune system to detect and destroy specific viruses, bacteria and other harmful substances, autoantibodies are antibodies that target a person's own healthy tissue. In the case of T1D, a misdirected autoimmune response attacks the pancreas and gradually destroys the organ's insulin-producing beta cells.

Without the hormone insulin the body cannot regulate its blood sugar levels, which can cause serious, long-term medical complications such as cardiovascular disease, nerve and kidney damage, and vision loss. Children (and adults) with T1D must monitor their dietary intake and exercise and take insulin injections, or use an insulin pump, daily to help control their blood sugar levels.

"Physically and psychologically, it's a very burdensome disease that needs to be managed every day over a lifetime," Dr. Vehik said.

For this TEDDY analysis, eligible children with increased genetic risk for T1D, were followed every three months, from the age of 3 months up to 15 years, for the development of a first-appearing autoantibody directed against pancreatic insulin-producing cells: glutamic acid decarboxylase antibody (GADA), insulin autoantibody (IAA), or insulinoma-associated-protein-2 autoantibody (IA2-2A). The researchers also looked for the subsequent appearance of a second autoantibody and further progression to T1D. Zinc transporter 8 autoantibody(ZnT8A) was only measured in children who developed an IAA, GADA, or IA-2A. These four different autoantibodies are so far the most reliable biological indicators of early T1D, before symptoms become apparent.

Of the 608 study participants—all testing positive for either a first-appearing IAA or GADA—more than half (336) developed a second autoantibody. Furthermore, 53% of these 336 children with a second antibody progressed to T1D within about 3.5 years. Only about 10% of the 272 children testing positive for a single autoantibody at the end of the follow-up for this study (Dec. 31, 2019) had transitioned to T1D.

Among the key study findings:

- All study participants had high-risk genotypes for T1D. However, those increased-risk children who also had a parent or sibling with T1D were more likely to develop a second-appearing autoantibody than those without a family history.
- The younger the child at the time they tested positive for a first autoantibody, the greater their risk for developing a second autoantibody. Conversely, the risk for T1D decreased if the first autoantibody appeared when the child was older.
- Children testing positive for a second autoantibody, regardless of

the type, had at least a five-fold increased risk of progressing to T1D, compared to children who stayed single autoantibody positive. IA-2A, as a second autoantibody, conferred the highest risk, compared with GADA, IAA, or ZnT8A.

- Risk of progression to T1D was influenced by how quickly the second autoantibody appeared. Emergence of a second autoantibody within a year of the first doubled the risk of progression to T1D. Children's likelihood of developing T1D declined as the months between the first and second-appearing autoantibodies increased.

Better stratifying the risk of progression from the start of autoimmunity to symptomatic disease could help diagnose T1D earlier and offers the opportunity to prevent diabetic ketoacidosis (DKA) and its serious complications by educating parents to watch for early signs, Dr. Vehik said.

"For instance, if a clinician knows that a young child testing positive for IA-2A as their second-appearing autoantibody will be at a higher risk to more rapidly progress to type 1 diabetes, they can reduce the risk of symptomatic onset of disease. Clinicians can also educate the parents about the early signs of disease, such as, weight loss, extreme thirst, more frequent urination, or other DKA symptoms," she said. "If that happens, the parents will know they should get their child to a doctor or hospital as soon as possible."

Specific antibody risk profiling can also help identify those at-risk children most likely to benefit from recruitment for T1D prevention trials, Dr. Vehik added.

Dr. Vehik next plans to build upon a previous TEDDY study linking viral behavior with T1D diabetes to test whether prolonged viral infections may environmentally trigger the transition from first- to

second-appearing islet autoantibodies in children genetically susceptible to diabetes.

More information: Kendra Vehik et al, Hierarchical Order of Distinct Autoantibody Spreading and Progression to Type 1 Diabetes in the TEDDY Study, *Diabetes Care* (2020). DOI: 10.2337/dc19-2547

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