A better diagnosis of rare diabetes to adapt treatment

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Diabetes affects more than 400 million people worldwide and is a major public health problem. Although commonly referred to as a single disease, it actually constitutes a group of metabolic disorders with hyperglycaemia as a common feature. Of all its forms, monogenic diabetes—due to a mutation in one of the genes involved in the

management of blood sugar levels—affects 1% to 4% of all cases of diabetes. Often confused with type 1 or type 2 diabetes, more than 90% of monogenic cases are misdiagnosed. A study carried out by scientists from the University of Geneva (UNIGE), the University Hospitals of Geneva (HUG), and the Lithuanian University of Health Sciences in Vilnius with more than 1,200 young diabetics allowed to accurately identify the proportion of monogenic diabetes in the whole pediatric diabetes population. Consequently, treatments were adjusted according to the genetic characteristics of the disease in order to improve patients' quality of life. The results that can be read in the journal *Diabetes*, highlight the need for precision medicine in the management of metabolic diseases.

Diabetes is defined by chronic hyperglycemia which may lead to dangerous complications. Type 2 diabetes and type 1 diabetes are the best known forms. Type 2 is often associated with obesity, while type 1 is an autoimmune disease where the immune system destroys the insulin-producing pancreatic beta cells. The form of diabetes studied here is called "monogenic," and is caused by a mutation in a single gene. In the majority of cases, these mutations prevent the beta cell from functioning properly and the disease often manifests during adolescence. Sometimes, however, the pancreas simply does not develop, and insulin must be administered to babies as soon as they are born.

Eleven new genes identified

Monogenic diabetes very often goes undiagnosed because its clinical features are quite similar to other forms of diabetes. Even if the symptoms are comparable, the cause is very different. "Lithuania has a register of all diabetic children, which also includes most of the young adults," says Valérie Schwitzgebel, professor at the Department of Paediatrics, Gynaecology and Obstetrics and co-coordinator of the Diabetes Centre of the UNIGE Faculty of Medicine and Head of the

Paediatric Endocrinology and Diabetology Unit at the HUG, who led this work. "We have thus carried out a large-scale epidemiological and population study."

The scientists first evaluated the presence of autoimmune antibodies, known markers of type 1 diabetes, in the 1209 children and young adults included in the cohort. A complete genetic analysis was then carried out on the 153 patients who did not have these antibodies or who had only anti-insulin antibodies, which can also develop from insulin treatment. "We were able to identify the gene mutation causing diabetes in 42 of them, a much larger number than expected," says Ingrida Stankute of the Lithuanian University of Medical Sciences. "In addition, almost 10% of the study participants who tested positive for autoimmune anti-insulin antibodies also had monogenic diabetes, indicating the need for accurate diagnosis."

While most patients had only one defective gene, many different mutations were identified, including eleven genes identified for the first time. "But do all these mutations produce the same effects? In the next step of our collaboration, we will therefore perform co-segregation studies in the patients' families and, and conduct experiments to analyse gene functions," says Valérie Schwitzgebel.

Adapting treatments adapted to mutations- a step toward precision medicine

In general, young diabetic patients, particularly when affected by type 1 diabetes, must follow a strict treatment based on insulin injections. "In many gene mutations however, beta cells can be stimulated through specific drugs, called sulfonylureas, which are much easier to administer than insulin injections and which have a much better effect on metabolism," explains Valérie Schwitzgebel. "Many of the patients

diagnosed, even the youngest, were thus able to switch to a lighter oral treatment, and some even stopped treatment altogether. This proves the need for precision medicine where treatment is tailored to the causes of the disease, not just the symptoms it triggers."

Toward a more systematic diagnosis

"In Geneva, we have already put this new evidence into practice," explains Jean-Louis Blouin, researcher at the Department of Genetic Medicine and Development at UNIGE Faculty of Medicine and at the HUG Department of Genetic Medicine. "We have developed a diagnostic test that includes the 40 plus genes that can lead to monogenic diabetes, and all diabetic children, who don't have autoimmune antibodies are tested." Even in adults, such a test would be useful, as monogenic diabetes is often falsely identified as type 2 diabetes, with important consequences in terms of management, comfort of life and costs for the health care system.

"Hyperglycaemia should therefore be considered as a symptom of various diseases, rather than a disease in itself, and different forms of diabetes should be better screened. The earlier the actual cause is identified, the sooner appropriate treatments can be initiated, minimizing the risk for long term complications," concludes Valérie Schwitzgebel.

More information: Ingrida Stankute et al. Systematic Genetic Study of Diabetic Youth in a Single Country Reveals the Prevalence of Diabetes Subtypes, Novel Candidate Genes, and Response to Precision Therapy, *Diabetes* (2020). DOI: 10.2337/DB19-0974

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