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Screening children for type 1 diabetes

Worth serious consideration, including further research

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Insulin was discovered in 1921, turning a death sentence into a chronic condition, and 100 years later it is still the only treatment for type 1 diabetes. But new approaches are emerging that offer children with this condition a different trajectory.

Type 1 diabetes is caused by autoimmune destruction of the β cells in the pancreatic islets, resulting in insulin deficiency, and is mostly sporadic (>85% of cases). Despite clinical advances, outcomes remain suboptimal, and as many as 70% of children in some countries (25% in the UK, 40% in US) are diagnosed only after life threatening diabetic ketoacidosis.[1]

The unexpected occurrence of type 1 diabetes causes psychological harm to both children and families, including depression, problems with adjustment, and stress.[2] Diabetic ketoacidosis additionally requires costly and intensive hospital management and is associated with serious complications, including cerebral oedema, neurocognitive deficits, shock, and, if untreated, death.[1]

Evidence is emerging of the benefits of diagnosing children with type 1 diabetes before they experience diabetic ketoacidosis. In an observational study of children and young people with type 1 diabetes from the US (n=3364), diabetic ketoacidosis at diagnosis was associated with worse glycaemic outcomes—a risk factor for long term complications—over 15 years of follow-up.[3] A more recent study of young people with diabetes (n=57 000) showed that absence of diabetic ketoacidosis at diagnosis predicted fewer episodes of severe hypoglycaemia and ketoacidosis after 10 years.[4] However, confounding by contributory factors cannot be excluded.

Children who develop type 1 diabetes have more frequent contact with health services in the year before diagnosis, yet the condition is often missed.[5] Campaigns to increase public and professional awareness have had minimal success.[6] A different strategy is needed, and we believe that nationwide screening should be considered, with robust clinical trials to evaluate potential benefits, harms, and costs.

Antibodies

Diabetes associated islet autoantibodies could be a useful screening tool, since a positive result in an asymptomatic child is strongly associated with later development of diabetes. In an analysis of data from three prospective cohort studies, 84% of children with two or more islet autoantibodies developed diabetes over 15 years of follow-up.[7]

A more recent study from Bavaria screened 90 632[8] children for islet autoantibodies at a median age of 3.1, followed by education, metabolic staging, and clinical follow-up for the 280 (0.3%) children with positive results. Of the 62 antibody positive children who developed diabetes either at the time of screening (n=26) or after 2.4 years of follow-up (n=36), only two had ketoacidosis (3.2%). This compares with an incidence above 20% among unscreened children who develop diabetes.[8]

Islet autoantibody testing is now commercially available in the US,[9] and the possibility of preventive intervention for people with positive results is emerging. In one placebo controlled trial (n=76; 55 aged ≤18 years), the anti-CD3 monoclonal antibody tepluzimab delayed diagnosis of diabetes by a median of 24 months (48.4 months to diagnosis *v* 24.4 months) in participants who were positive for islet autoantibodies and had raised glucose levels below the threshold for diabetes.[10]

Type 1 diabetes meets several of Wilson and Jungner's criteria for screening[11]: it is an important condition, and incidence is increasing by 4% worldwide each year. Data from Bavaria, as well as observational studies such as Teddy (The Environmental Determinants of Diabetes in the Young), suggest that screening can be acceptable to families.[8,12] In Teddy, children identified through a screening and monitoring strategy that combined genetic risk with islet autoantibody testing reported significantly better diabetes specific quality of life over the first year after diagnosis than matched community controls diagnosed without screening.[12] Their parents reported significantly lower parenting stress.

Age 3-4 years has been suggested as the best time to screen children using islet autoantibody testing,[13] allowing time for interventions such as parental education and monitoring to reduce the risk of diabetic ketoacidosis in those with positive results. However, this strategy would miss the youngest, and often sickest, children who develop diabetes, as well as those who develop autoantibodies later in childhood. Adding genetic data to autoantibody screening may increase the proportion of children identified as high risk, including the youngest children.[14] But many children considered genetically high risk will never develop type 1 diabetes, raising concerns about the acceptability of genetic screening.

The time lag between screening for islet autoantibodies and diagnosis is a further concern. Evidence is needed on how best to follow up children with antibodies, and when to retest those with only one type of antibody, who have a relatively low risk (10-15%) of diabetes.[7] More precise predictors of diabetes onset are needed to support clinical pathways and allow fully informed shared decision making with families.

More research is required to identify the most effective and cost effective screening strategies, and most importantly to quantify the balance of benefits and harms, which include raised anxiety for children and parents and the burden associated with a follow-up programme for children found to be at risk. Trials should include rate of hospital admission at diagnosis as an outcome, as well as short and long term psychological and metabolic outcomes. A hundred years after the discovery of insulin, the evaluation of screening should be a research priority.

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