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Research Article

When is Screening for Type 1 Diabetes in Children Justified?

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Abstart

Background: Screening to find individuals with high riskof developing Type 1 diabetes (T1D) is needed to recruit participants for prevention trials and studies to preserve residual beta cell function at diagnosis. Screening may also decreasethe incidence of diabetic keto-acidosis (DKA) at diagnosis. However screening may cause anxiety and decrease quality of life for patients and their relatives. The aim of this study was to get a picture of how screening followed by development of T1D can be experienced.

Material and methods: Two boys, A and B, and a girl Cwere identified as high risk individuals via determination of autoantibodies, They developed T1D at the age of 7, 12 and 14 years. The parents of the boys, and the now adult female, gave their views.

Results: The mother of Boy A was very anxious during years before the T1D diagnosis, and got psychiatric problems with difficulties to work long periods. Both parents emphasized that they would have preferred not to know that their son might get T1D. Already within two years blood glucose balance of Boy B deteriorated, related to his difficulties to accept his disease.The woman C told that she for 6 years after diagnosis could not accept her disease.

Conclusions: Screening for risk of getting T1D sometimes have negative consequencies. Screening is justified when trials are offered, and in certain populations when other methods to prevent DKA have failed. When screening otherwise is justified needs careful evaluation.

Keywords: Type 1 diabetes; Children; Screening; Keto-acidosis; C-peptide; Psychological problems

Introduction

The cause of Type diabetes is unknown. Genetic predisposition is important [1] together with environmental factors [2]. The clinical manifestation of Type 1 diabetes is preceded by a long asymptomatic period. when autoantibodies in combination with genetic factors will predict the disease [3]. The process is illustrated in Figure 1, presented 1981, and later followed by more wellknown diagrams [4]. As well as celiac disease nowadays is diagnosed based on existing autoantibodies, sometimes without any clinical symptoms or signs, it has been proposed that Type 1 diabetes could be said to have different stages [5], being clinically manifest in stage IV. Screening to find individuals in stage I-III is needed to recruit participants into prevention trials, studies that are extremely important [6,7]. Screening has also shown to decreasethe risk for Diabetic Keto-Acidosis (DKA) at diagnosis, in high risk individuals motivated for participation in studies [8,9]. It has also been proposed that early diagnosis of T1D might preserve residual beta cell function [10], although the evidence for this can be questioned. Thus there are many good reasons to screen to find high risk individuals, but screening has also disadvantages. Very large populations have to be sceened to find high risk individuals fulfilling criteria for participation in prevention trials [11] which consumes research resources. Unless the specificity is extremely high a large number of individuals may get worried by mistake, while a low sensitivity will give a false security. Another problem is the anxiety caused by informing patients, and especially parents that there child has a high risk of developing a serious disease [12]. This is especially serious if nothing is offered to try to prevent the disaster. In this study the aim was to get a picture of how the screening process and later development of Typ 1 diabetes can be experienced.

Material an Methods

Two boys, A and B, identified with high genetic HLA risk as newborns were included in the Prodia study, a pilot trial using probiotics for prevention of T1D [13]. They developed autoantibodies

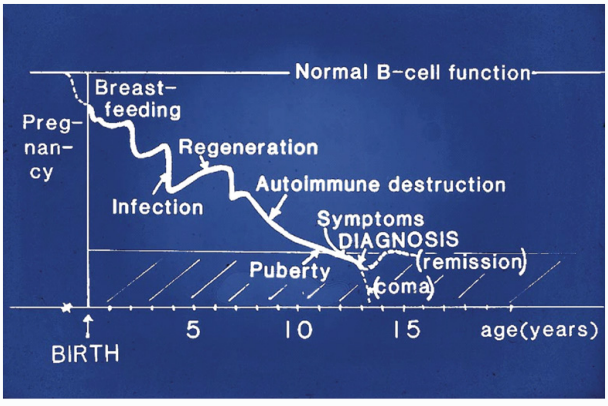

Figure 1: Gradual development of Type 1 diabetes, presented by Johnny Ludvigsson 1981 at Nordic Diabetes Symposium in connection with the Annual Meeting for the Scandinavian Society for the Study of Diabetes.

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within 24 months. BoyA got the diagnosis T1D at the age of 7 years, without symptoms. He was in partial remission for two years but then with gradually increasing insulin requirement. Boy B got his diagnosis at 12 years of age when he was screened for inclusion in a prevention trial. He was metabolically stable for two years, but thereafter with less good metabolic control than average patients. A woman,C,participated as a child in ABIS (All Babies in Southeast Sweden) [14]. She got multiple autoantibodies during childhood and she and her parents were informed about her high risk when she at the age of 10 was included in a substudy of ABIS on high risk individuals [15]. She was diagnosed with T1D two years later without symptoms. Nowadays she works as influencer and gives lectures in schools. The parents of the two boys have been interviewed about their opinion and experience of getting the early information on high risk if their child to get Type 1 diabetes an its consequencies, an the young woman aged 20 years has described her opinion and experience.

Results

The mother of Boy A was very anxiousfor years before the T1D diagnosis, and got psychiatric problems with difficulties to work certain periods. Both parents expressed clearly that they would have preferred not to know for years that their son had high risk of getting T1D. Boy B was initially metabolically stable but when his blood glucose balance deteriorated he has had difficulties to accept his disease as he has never felt that the treatment saved him from disease symptoms. The woman C tells that she for long time could not at all accept her disease. She had felt completely healthy at diagnosis, could not understand why she was told to have a serious disease, but rather felt that ”the treatment made her ill”.She hated the injections and other restrictions and refused to say the word ”diabetes”. For 3-4 years she could omit insulin doses and blood glucose still rarely passed > 8 mmol/l. Therefore she also felt different from other diabetic children who were suspicious on her ”so called diabetes”. It took 6 years for her to finally accept her disease and the hateful treatment.

Discussion

These three cases illustrate how early information about high risk of getting T1D can lead to quite negative consequencies. The possible benefits of diagnosis during stage III, with multiple autoantibodiesand gradual glucose intolerance but without symptoms, should be weighed against the negative psychological consequences of knowing the risk sometimes for many years. People not knowing so much about T1D do not seem to worry when participating in a prospective trial like ABIS [14]. In ABIS, a general population without any genetic predisposition to get T1D, we did not actively inform about laboratory results unless asked for according to the decision of the Research Ethics Review Board. The parents were told that they could get information and ask fortheir child´s risk, but less than one promille ever did. But studies where participants have been actively informed show that parents of high risk children get worried, and even more so in families with T1D members, probably as they know the disease and its negative consequencies. Their anxiety lasts for years, and this burden, as well as the burden of getting the diabetes diagnosis a long time before clinical manifestation of symptoms, sometimes making it difficult for the child to accept the disease, has to be weighed against the value of screening. It is expected that diagnosis in stage III, with multiple autoantibodies and abnormal glucoe intolerance but no clinical symptoms or signs, means better beta cell function and beta cell preservation. However, diagnosis during this stage does not necessarily mean better beta cell function at a certain age than if the child had got the diagnosis later when stage IV starts, with clinical symptoms (Figure 2). Age-matched controls who get clinical disease (stage IV) at the same age as individuals diagnosed during stage III, just with abnormal OGTT, can be expected to have lower C-peptide because of a more pronounced disease process.Diagnosis in early stage III, means that the patientwill get a heavy treatment with insulin, glucose monitoring, restrictions in life style, sometimes for years, when he/she otherwise would have lived as ”healthy” with good quality of life. Thus the girl C in this study might have had years being ”healthy”, without T1D, as she for several years could omit insulin without gettinghigh blood glucose, and we do not know whether her C-peptide at 18 years of age was better because of diagnosis at 12 years of age, than if she hade been diagnosed at age 15 with clinical symptoms. It is valuable to avoid severe keto-acidosis (DKA) at onset, but there are other possibilities to decrease incidence of DKA with information campaigns [16] without creating the negative consequencies of screening. Furthermore DKA at diagnosis is far from completely avoided by screening [8], as there may even be a risk that screening gives a false security, while rapid progression may cause serious disease also in these indiviuals. Early screening is necessary and valuable to find participants for secondary prevention trials and then justified. The same may be true when there are safe, efficaceous interventions to preserve beta cell function at diagnosis. Some parents may also want to get a sibling tested for autoantibodies, when there already is T1D in the family. No autoantibodies will then be calming, while autoantibodies just confirm what the parents already feared, without increasing their anxiety. This study has limitations: Three cases cannot be generalized to all others in the same position. Most probably there are many who do not worry very much about the high risk, and who may be grateful for the screening also after T1D diagnosis, as their child avoided serious symptoms and DKA at diagnosis. However, the two boys are not selected but are the only two cases of children in the Prodia study who developed T1D. The girls is one of few cases in the ABIS study where information was given before diagnosis.

Conclusions

Screening for risk of getting T1D sometimes have negative consequencies. Screening is justified as part of research when trials are offered, and in certain populations when other methods to prevent

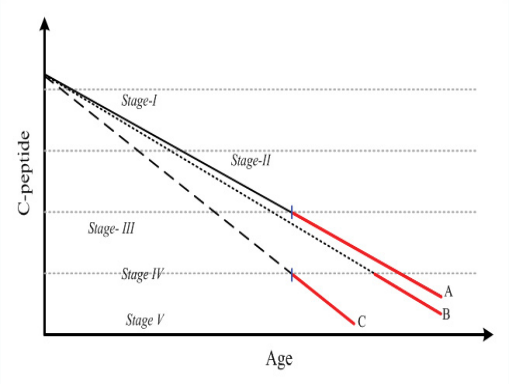

Figure 2: Patients diagnosed via screening (A) get their diagnosis of T1D earlier, with higher C-peptide, than patients (B) who have lost more C-peptide when they finally get clinical symptoms, but their C-peptide decline may be the same. Age-matched patients (C) who get their diagnosis based on clinical symptoms at the same age and time as patients diagnosed by screening have had a more rapid and serious disease process with lower C-peptide, and can be expected to have shorter time with residual beta cell function.

DKA have failed. When screening otherwise is justified needs careful evaluation.

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References

1. Rewers M, Ludvigsson JEnvironmental risk factors for type 1 diabetes. Lancet. 2016;387(10035):2340-8.
2. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. Lancet. 2016;387(10035):2331-9.
3. Ferrat LA, Vehik K, Sharp SA, Lernmark Å, Rewers MJ, She JX, et al. TEDDY Study Group; CommitteesA combined risk score enhances prediction of type 1 diabetes among susceptible children. Nat Med. 2020;26(8):1247-55.
4. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med. 1986;314:1360-8.
5. Jennifer J Couper, Michael J Haller, Annette-G Ziegler, Mikael Knip, Johnny Ludvigsson, Maria E Craig, International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2014. Phases of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2014;15:18-25.
6. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019;381(7):603-13.
7. Ziegler AG, Achenbach P, Berner R, Casteels K, Danne T, Gündert M, et al. Oral insulin therapy for primary prevention of type 1 diabetes in infants with high genetic risk: the GPPAD-POInT (global platform for the prevention of autoimmune diabetes primary oral insulin trial) study protocol. BMJ Open. 2019;9(6):e028578.
8. Elding Larsson H, Vehik K, Bell R, Dabelea D, Dolan L, Pihoker C, et al. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. Diabetes Care. 2011;34(11):2347-52.
9. Nakhla M, Cuthbertson D, Becker DJ, Pacaud D, Ludvigsson J, Knip M. Legault LDiabetic Ketoacidosis at the Time of Diagnosis of Type 1 Diabetes in Children: Insights From TRIGR. JAMA Pediatr. 2021:e205512.
10. Steck AK, Larsson HE, Liu X, Veijola R, Toppari J, Hagopian WA, et al. and the TEDDY Study Group. Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls. Pediatr Diabetes. 2017;18(8):794-802.
11. Diabetes Prevention Trial-Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med. 2002;345:1685-91.
12. Melin J, Maziarz M, Andrén Aronsson C, Lundgren M, Elding Larsson H. Parental anxiety after 5 years of participation in a longitudinal study of children at high risk of type 1 diabetes. Pediatr Diabetes. 2020;21(5):878-89.
13. Ljungberg M, Korpela R, Ilonen J, Ludvigsson J, Vaarala O. Probiotics for the prevention of beta cell autoimmunity in children at genetic risk of type 1 diabetes--the PRODIA study. Ann N Y Acad Sci. 2006;1079:360-4.
14. Ludvigsson J, Ludvigsson M, Sepa A. Screening for prediabetes in the general child population: maternal attitude to participation. Pediatr Diabetes. 2001;2(4):170-4.
15. Åkerman L, Ludvigsson J, Swartling U, Casas R. Characteristics of the pre-diabetic period in children with high risk of type 1 diabetes recruited from the general Swedish population-The ABIS study. Diabetes Metab Res Rev. 2017;33(6).
16. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes Care. 1999;22(1):7-9.