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Presentation and characteristics of children with screen-detected type 1 diabetes: learnings from the ELSA general population pediatric screening study

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ABSTRACT

Introduction We describe the identification and management of general population screen-detected type 1 diabetes (T1D) and share learnings for best practice.

Research design and methods Children diagnosed with T1D through a general population screening initiative, the EarLy Surveillance for Autoimmune diabetes (ELSA) study, were reviewed and described.

Parents provided written, informed consent for inclusion in the case series.

Results 14 children with insulin requiring (stage 3) T1D are described. These cases offer unique insights into the features of screen-detected T1D. T1D is identified sooner through screening programs, characterized by absent/short symptom duration, median presenting glycated hemoglobin 6.6% (49 mmol/mol) and insulin requirements<0.5 units/kg/day. ELSA identified four children at stage 3 and another 4 progressed within 4 months of ELSA completion, including two single seropositive children. Six children developed stage 3 T1D prior to ELSA completion, including two children (14%, n=2/14) with diabetic ketoacidosis prior to confirmed antibody status.

Conclusions There are three main learnings from this case series. First, T1D identified through screening is at an earlier stage of its natural history and requires personalized insulin regimens with lower total daily insulin doses. Second, single autoantibody seropositivity can rapidly progress to stage 3. Finally, insulin requirement can manifest at any stage of the T1D screening pathway, and therefore early education around symptom recognition is essential for families participating in screening programs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ As increasing numbers of children are screened for type 1 diabetes (T1D), understanding their transition from research pathway into clinical care is important.

WHAT THIS STUDY ADDS

⇒ We describe the identification and management of the first 14 stage 3 T1D cases from the UK's EarLy Surveillance for Autoimmune diabetes (ELSA) study to share learnings for best practice. This paper adds three key messages to the previous literature reporting clinically milder phenotype of screen-detected T1D.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These learnings from the ELSA study are important for healthcare professionals and policymakers to raise awareness and increase confidence in managing presymptomatic T1D.

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune condition caused by destruction of the insulin-producing pancreatic islet beta cells.[1] Screening for islet-specific autoantibodies (Aab) in otherwise healthy children enables early identification of T1D up to 15 years before symptomatic onset of disease.[2] The presence of a single Aab associates with a 14.5% progression to insulin requiring T1D over a 10-year period.[3] However, the presence of two or more Aab indicates a lifetime certainty of requiring insulin and has been termed T1D even before the onset of hyperglycemia.[4 5] Children identified with two or more Aab can be subsequently staged with oral glucose tolerance testing (OGTT): normoglycemia (stage 1), dysglycemia (stage 2), non-insulin requiring hyperglycemia without osmotic symptoms (stage 3a) and insulin requiring with symptoms (stage 3b).[5]

Pediatric T1D screening studies are being set up internationally, including the EarLy Surveillance for Autoimmune diabetes

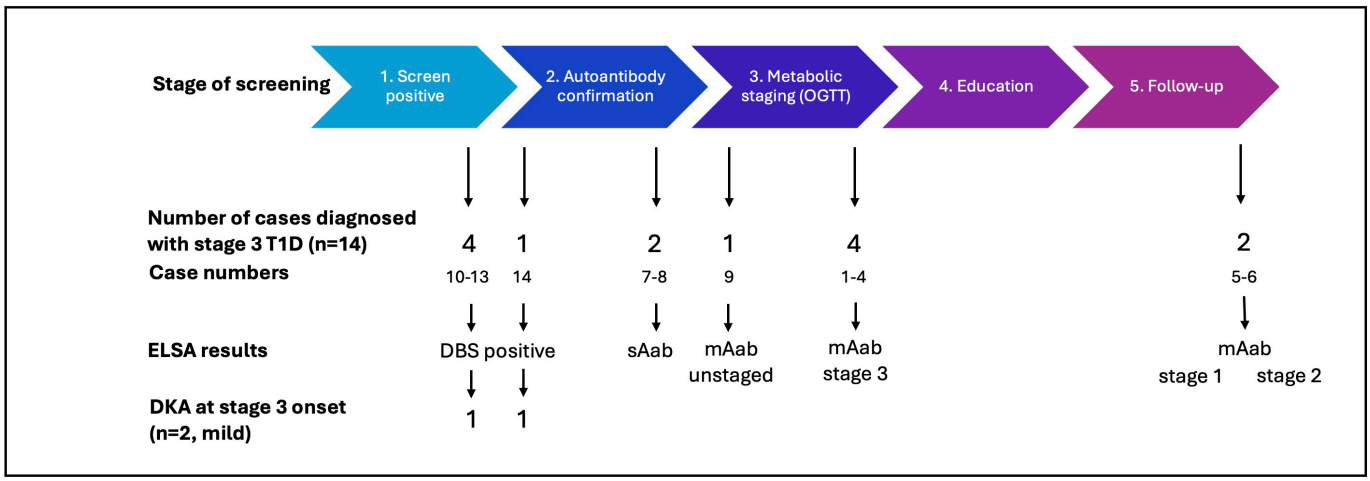

Figure 1 Summary of stage 3 cases identified in the ELSA study. Figure outlining where stage 3 cases were identified during the ELSA study. Four children were diagnosed after study enrollment and prior to DBS results notification (cases 10–13). One child was diagnosed following DBS results notification but prior to venous autoantibody (Aab) confirmation (case 14). Of these, two children had mild DKA. Two children progressed to stage 3 within 2 months of single Aab results notification (cases 7–8) and one child progressed to stage 3 prior to metabolic staging (case 9). Four children had stage 3 T1D from the ELSA OGTT (cases 1–4). Two children progressed from presymptomatic to symptomatic T1D within 6 months of ELSA staging (cases 5–6). DBS, dried blood spot; DKA, diabetic ketoacidosis; ELSA, EarLy Surveillance for Autoimmune diabetes; mAab, multiple autoantibody positive; OGTT, oral glucose tolerance testing; sAab, single autoantibody positive; T1D, type 1 diabetes.

(ELSA) study in the UK.[6] Screening achieves a fivefold reduction in diabetic ketoacidosis (DKA),[7] in addition to shorter duration or absence of symptoms, lower glycated hemoglobin (HbA1c) and lower initial insulin requirements.[8] In contrast, up to 58% of children identified in usual care present in DKA,[9] frequently due to late or missed diagnoses.[10–12]

As increasing numbers of children are screened (>200,000 internationally),[6] the transition of screen-detected cases from research into clinical care becomes relevant to healthcare providers. We wanted to describe children diagnosed at stage 3 T1D from the UK ELSA study and share key learnings for best practice management of screen-detected T1D.

RESEARCH DESIGN AND METHODS

The ELSA study aims to explore the feasibility and acceptability of screening children aged 3–13 years for T1D (www.elsadiabetes.nhs.uk) (figure 1). Recruitment approaches include home-testing, community clinics (schools, primary care, community centers) and hospitals and commenced in November 2022. The screening test is the RSR Limited 3-screen ELISA for anti-islet antigen 2 (IA-2A), anti-glutamic acid decarboxylase (anti-GAD) and anti-Zinc transporter 8 (ZnT8) Aab[13] undertaken on a dried blood spot (DBS) collected on filter paper. Those screening positive on the DBS test are offered a confirmation on a venous blood sample measuring IA-2A, insulin, GAD and ZnT8 Aab. Children with a single Aab are followed up yearly with Aab testing in the follow-on Innovative approach towards understanding and arresting type 1 diabetes (INNODIA) study.[14] Those with two or more Aab are staged with OGTT. Those who are stage 3 are referred directly into clinical care for insulin initiation, and those with stages 1 and 2 are signposted to the follow-up INNODIA program[14] for 6 monthly monitoring until they progress to stage 3 T1D.

A patient and public involvement group, comprising both parents and children, contributed to the design of the ELSA study and development of participant information including leaflets, videos and educational resources.

We obtained written informed consent from parents for inclusion in the case series. Stage 3 cases identified between recruitment onset and April 2024 are included. Demographic data, including child's ethnicity, postcode for Index of Multiple Deprivation (IMD)[15] and family history of diabetes, were collected at time of entry to the ELSA study. We contacted the child's lead consultant pediatrician who provided discharge summaries, clinic letters, laboratory investigations and ambulatory glucose profiles reports since T1D diagnosis. Parents were contacted to clarify the case histories. T1D and DKA diagnoses met International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines.[16] HbA1c≥6.5% (≥48 mmol/mol) indicates stage 3 T1D. Children diagnosed with T1D are managed by a multidisciplinary care team, including pediatric consultant, diabetes specialist nurse, dietician and access to clinical psychology services, as recommended by National Institute for Health and Care Excellence (NICE) guidelines.[17]

RESULTS

Over 10,000 children have completed the ELSA study at the time of preparing this case series in June 2024. We report on the first 14 cases of stage 3 T1D identified during or following ELSA study participation. Of these,

71% were boys, median age 8 years (range 3–12 years), 86% were White European ethnicity (British, Irish or other) and 86% had a family history of T1D (first-degree or second-degree relative). Of the 10 children living in England, the median IMD level was 7 (range 1–9) (2 children lived in Northern Ireland, 1 in Scotland and 1 in Wales).

Of the 14 stage 3 T1D cases, 6 were diagnosed prior to ELSA study completion, 4 were screen detected as stage 3 at the time of ELSA metabolic staging and 4 progressed within 4 months of ELSA staging (see figure 1 and online supplemental table 1 for case summaries).

Three key messages emerged: (1) screening identifies stage 3 T1D early, (2) single Aab can progress to stage 3 and (3) insulin-requiring stage 3 T1D emerges at any point of the screening pathway.

SCREENING IDENTIFIES CHILDREN WITH EARLY STAGE 3 T1D

Screen-detected T1D identifies children at an earlier stage of its natural history. Twelve children (cases 1–12, 86%) had absent or short (typically 1–2 weeks) duration of osmotic symptoms, a median HbA1c of 6.6% (range 5.5%–15.1%) (49 mmol/mol (range 37–142 mmol/mol)) and avoided DKA.

Of the ELSA stage 3 screen-detected cases (n=4), two were stage 3a (asymptomatic) and two stage 3b (symptomatic),[5] all with HbA1c<6.3% (< 45 mmol/mol). The stage 3a cases (1 and 2) avoided hospital admission and commenced continuous glucose monitoring (CGM) under pediatric diabetes specialists. Case 1 progressed to stage 3b after 6 months and started multiple daily injections (MDI) specified dose with evening meal (total daily dose (TDD)<0.5 units/kg/day). Case 2 never experienced osmotic symptoms; instead, following increased CGM time above range, commenced insulin aspart set-dose with breakfast and split set-dose with evening meal (TDD<0.5 units/kg/day).

ELSA stage 3b cases had intermittent osmotic symptoms prior to ELSA OGTT, but home capillary blood glucose (CBG) readings were <11.1 mmol/L. Case 3 was admitted for one night and started MDI (TDD=0.3 units/kg/day). Following discharge, frequent hypoglycemia led to dose reduction and split dosing with evening meal. Case 4 had a weekend admission (three nights) following stage 3b identification. Insulin glargine commencement (1 unit) in hospital led to hypoglycemia and no further insulin was given during admission. Insulin aspart 0.5–1 unit with evening meal (1:20) (TDD<0.5 units/kg/day) was prescribed on discharge.

Follow-up of those identified at risk facilitates earlier stage 3 identification

One stage 2 (case 5) and one stage 1 child (case 6) progressed to stage 3b within 6 months of ELSA completion and prior to research follow-up. One parent (case 5) declined INNODIA follow-up and was referred to the local diabetes team, with remote support including joint consultation with the ELSA clinical team. Recommendations for stage 2 management in clinical care followed the European guidelines, included CBG meter provision and training, 3 monthly HbA1c and intermittent CGM.[18 19] There were frequent telephone contacts and one pediatric assessment unit attendance for hyperglycemia which resolved within 2 hours without insulin. A few months later, after 2 days of osmotic symptoms, stage 3b T1D was diagnosed, avoiding DKA and overnight hospital admission, and ultra-rapid acting insulin aspart specified dose commenced with evening meals (<0.5 units/kg/day).

SINGLE AAB CAN PROGRESS TO STAGE 3

Two single Aab-positive children developed stage 3b T1D within 2 months of completing ELSA. Case 7 had intermittent osmotic symptoms which progressed during the ELSA study. Following antibody results notification, the ELSA pediatrician referred for urgent same day assessment and insulin was commenced. Case 8 developed a viral illness 1 month after ELSA and following a 2-day history of osmotic symptoms and high home CBG readings, parent contacted the local pediatric diabetes team for insulin initiation on an outpatient basis.

Insulin-requiring stage 3 T1D emerges at any stage of the screening pathway

Having entered the ELSA study, two cases presented with stage 3b T1D in DKA prior to completion. Case 13 developed osmotic symptoms prior to ELSA DBS results notification (screened positive) leading to emergency department attendance. This was mild DKA (pH 7.21, ketones 6.4 mmol/L) based on ISPAD 2022 criteria (mild DKA pH 7.2–7.3)[16] with overnight admission. MDI regimen was commenced but due to frequent hypoglycemia, automated insulin delivery was started within 4 months of diagnosis, leading to an HbA1c of 6.5% (47 mmol/mol).

Case 14 screened positive in an ELSA community clinic. Language and travel barriers caused delays in confirmatory Aab testing and two appointment non-attendances. Parental concerns regarding polydipsia and increasing fatigue led to appropriate attendance at the emergency department. The child was diagnosed with mild DKA (pH 7.21, ketones 6.8 mmol/L),[16] with HbA1c 12.9% (118 mmol/mol) and admitted for 8 days for insulin initiation and structured education due to significant language barriers. The child was discharged on TDD>0.5 units/kg/day and HbA1c improved to 5.5% (37 mmol/mol) within 3 months of diagnosis.

DISCUSSION

This case series illustrates how screening facilitates earlier identification of stage 3 disease, reminds us that children with single Aab rapidly progress to requiring insulin, and hence benefit from education and follow-up, and finally, that the requirement for insulin can manifest at any stage of the T1D screening pathway. These cases offer

unique insights into the characteristic features of screen-detected T1D.

The strength of this early cases series is the description of the first 14 stage 3 cases emerging from the ELSA study, which provide important learnings for clinicians managing early T1D and for organizations delivering population screening programs. While the clinically milder phenotype of screen-detected T1D is well described by Fr1da[8] and others,[20–22] our three messages build on this literature and offer specific examples for best practice management. As increasing numbers of children are screen detected and if screening programs are nationally adopted as in Italy,[23 24] the research protocols will need to integrate into pediatric clinical services.[25] Hence, there is an urgent need to raise awareness and increase healthcare professionals' confidence managing these presymptomatic T1D cases.

Screening facilitates early stage 3 diagnosis

Screening, combined with education and follow-up, is the most effective way to prevent DKA.[7 22 26] Fr1da (German general population T1D screening study)[27] has achieved the lowest DKA rate at 2.5% (n=3/128)[7 8] and in this case series, all eight cases completing the ELSA study avoided DKA. Long-term benefits of screen-detected T1D include improved glucose control for at least the first 5 years after diagnosis[28 29] and reduced parental stress at insulin commencement compared with diagnosis through usual care.[30]

Further, screen-detected T1D leads to identification at an earlier stage of its natural history. ELSA and Fr1da's glucose metrics at stage 3 are comparable,[8] including HbA1c (6.6% (49 mmol/mol) vs 6.8% (51 mmol/mol)), fasting glucose (4.7 vs 5.3 mmol/L) and proportion not requiring insulin immediately (86% vs 72%). Compared with unscreened populations (Europe/UK), HbA1c at diagnosis (without DKA) ranges from 10.1% t0 10.5% (87–91 mmol/mol)[8 31] and 98% require insulin immediately.[8] Our series supports Fr1da's findings that screen-detected cases experience a clinically milder presentation at stage 3.[8]

ELSA study participation expedited stage 3 diagnosis in seven cases. When stage 3 T1D diagnosis occurred independently of ELSA participation (n=5), all children had a sibling or parent with T1D. Hence, osmotic symptom emergence combined with access to home CBG testing confirmed hyperglycemia and led to appropriate healthcare attendance. Four children avoided overnight admission, largely due to a first degree relative with T1D (sibling or parent) already educated in glucose monitoring and insulin administration.

Detection in presymptomatic stages identifies individuals for immunoprevention trials and treatments. The first agent licensed in the USA, teplizumab,[32] which delays stage 3 onset,[33] is undergoing NICE consultation for UK licensing, with a decision expected in November 2024.[34]

Single Aab progress to stage 3

The risk of progression to stage 3 T1D for single islet Aab is 14.5% (95% CI: 10.3% to 18.7%) in 10 years.[3] Factors associated with increased rate of progression include IA-2A seropositivity (40.5% progress to T1D within 10 years (CI: 17.7% to 63.3%)),[3] younger age at Aab detection[35 36] and high T1D genetic risk score.[35 37] In preschool children, a single seropositive Aab is most likely to progress to multiple within 2 years.[35 38] Yet, single Aab results present uncertain significance and may provoke unnecessary health anxiety for a transiently occurring Aab. As such, single Aab results are not reported or followed-up in Fr1da or European action for the Diagnosis of Early Non-clinical Type 1 diabetes For disease Interception (EDENT1FI), the European population screening collaboration. In ELSA, our experience shows Aab families benefit from education similar to multiple seropositivity, including T1D symptom counselling and follow-up to risk stratify according to Aab status.[35] Acceptability assessments via qualitative interviews are ongoing to explore the benefits and harms of single Aab notification.[39] The recent Juvenile Diabetes Research Foundation (JDRF) guidance recommends monitoring for at least 2 years after initial seroconversion. For preschool children (<3 years), 6 monthly metabolic monitoring is recommended for 3 years, whereas for children≥3 years, Aab status and metabolic monitoring are recommended annually for 3 years.[40]

Follow-up of screen-detected T1D supports earlier stage 3 detection

Follow-up after screening is recommended for appropriate timing of insulin initiation, DKA prevention at onset and to facilitate entry to immunoprevention trials.[5 7 41] European guidelines[18] and an international consensus report[40] are now published for managing pre-stage 3 T1D and both recommend specialist follow-up according to T1D stage and age of child. To reduce invasive procedures and improve follow-up adherence,[42] OGTTs are recommended less frequently than former research protocols (eg, INNODIA) and replaced with HbA1c and random plasma glucose 3–6 monthly. All multiple Aab-positive children should receive a CBG meter and training, with testing recommended for osmotic symptoms or febrile illness.[18] This provides a rapid point-of-care test for families to inform appropriate health-seeking behaviors. In our experience, selected cases also benefit from clinical follow-up. As exemplified by case 5, some children at stage 2 who are symptomatic cannot wait for 12 monthly OGTT through INNODIA. There is need for clinical support for these families in between research visits. Our post-ELSA pathway recommends referral for children at stage 2 with intermittent osmotic symptoms, or if the family decline research follow-up, for example, due to geographical barriers. This facilitates safe management of presymptomatic T1D from experienced professionals and mitigates families' distress.

Arguably, a landmark advance is the release of an internationally authorized SNOMED code for 'presymptomatic T1D (disorder)' (1290118005), recommended for inclusion in the child's electronic health record. The International Classification of Diseases—10 similarly recognizes presymptomatic T1D with the following codes:
1. E10.A0 (T1D, presymptomatic, unspecified).
2. E10.A1 (T1D, presymptomatic, stage 1).
3. E10.A2 (T1D, presymptomatic, stage 2).

These codes aim to facilitate earlier diagnosis for high-risk children (Aab-positive stage 1–2) at future healthcare contacts.

Managing early stage 3

Screen-detected T1D cases have lower insulin requirements than standard initiation protocols. The Environmental Determinants of Diabetes in the Young (TEDDY), the largest prospective study of children genetically predisposed to T1D[43] and Fr1da, showed this correlated with higher C-peptide at stage 3 detection and persists for up to 1 year after diagnosis, indicating partial remission phase.[8 20 44] As such, screen-detected cases require personalized insulin initiation plans, with reduced TDD and less frequent MDI. Here, the priority is hypoglycemia avoidance. A set bolus given with the highest carbohydrate load of the day (usually evening meal) may suffice if basal insulin is not commenced. A recent Lancet comment recognized lack of empirical evidence for insulin initiation in early stage 3 and recommended a treat to target approach to match the child's physiology, including basal commencement for nocturnal hyperglycemia or prandial insulin for recurrent postprandial hyperglycemia>11.1 mmol/L (>200 mg/dL) for >2 hours or high carbohydrate portions.[45]

Insulin-requiring stage 3 T1D can emerge at any time during the screening pathway

Two main learning points emerged from the DKA cases (14%, n=2/14). First, case 14 had known risk factors for DKA, including no family history of T1D, minority ethnicity and high deprivation[46 47] demonstrating need for symptom vigilance from screening enrollment.[11] An important new finding from ELSA is that parents may enter a screening program due to T1D symptom concerns. In ELSA, from the first 10,202 children screened, 6 (0.06%) were diagnosed stage 3 (1 DKA) prior to study completion (Aab confirmation or OGTT), while in Fr1da, 19 out of 90,632 (0.02%) children were diagnosed stage 3 prior to Aab confirmation.[7] Evidently, screening protocol timelines must be strictly adhered to and facilitate timely transition between follow-ups (screening test, confirmation and staging). Also, signposting and counselling must be incorporated early in any screening program to ensure medical services are appropriately accessed when symptoms arise. This ensures population screening is reserved for risk identification for the asymptomatic target population. However, screening also offers important opportunities to educate about symptoms of T1D. In ELSA, this information is presented at screening enrollment and again by a healthcare provider at results notification to facilitate earlier stage 3 diagnosis. Families are advised not to wait for screening results if there are immediate concerns about emerging T1D. These essential safety measures must be integrated into population screening programs.

In conclusion, we report three key messages emerging from the first 14 stage 3 T1D cases detected during and following participation in the UK's pediatric screening study (ELSA). Screening, education and monitoring facilitate earlier stage 3 diagnosis, characterized by milder clinical presentation and personalized insulin regimens with lower insulin requirements. Single Aab can progress to stage 3, and therefore benefit from follow-up. Finally, education, including early symptom recognition, is essential to avoid late presentation for children enrolled in a screening program. We envisage that these learnings will support best practice dissemination at a time when screening studies are contributing to increasing numbers of T1D diagnoses.

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Patient consent for publication Not applicable.

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