NON GENETIC RISK FACTORS OF TYPE 1 DIABETES IN TODDLERS

Thesis

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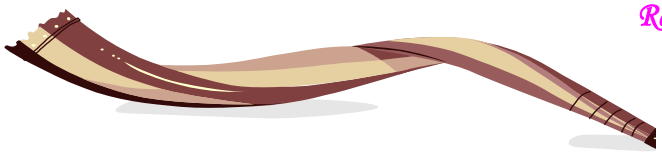

ABSTRACT

Type 1 diabetes (T1D) is the most common endocrine–metabolic disorder of childhood. Risk factors for type I diabetes include genetic and non–genetic factors). **Aim of the work:** To study possible non genetic risk factors that might have caused T1D in a group of infants and toddlers (6 months to 2 years of age) presenting to the Diabetes, Endocrine, Metabolic, Pediatric Unit (DEMPU) of Cairo University Children's Hospital. **Methods:** We used a pre-coded questionnaire filled out by the parent or care-giver to derive the following information: personal history, details of present illness, past history of illnesses or viral infections, vaccination history (compulsory and optional), family history and nutritional history. We compared the results of these children with an equal number of healthy, non-diabetic controls. **Results:** In total, we reviewed the histories of 200 diabetic children how had developed DM type 1 during infancy and an identical number of controls. All the children with T1D presented with polyurea, polydypsia and weight loss while 74% presented with DKA. A male predominance in T1D cases (67%) was noted in this young age group. Environmental risk factors that appeared to be significant in our study were: room number <3, unclean environments, receiving Hib &Rota virus vaccination (64% compared to 22.5% in controls, *0.003p*=), additional doses of polio vaccination above compulsory number (*p*=0.001), repeated viral infections, history of dehydration, a positive family history of type II diabetes (26.5% compared to 6.0% in controls, *p*= 0.001), and a family history of gestational diabetes (1% compared to 6 %in controls). Nutritional history revealed that 96% of cases were breast fed (but none exclusively), about 46% were introduced to cow milk and Carbohydrates at 4-6 months (history of cow milk introduction before 1st year of life (99.0% in cases compared to 84.0 % in controls. *p*= 0.001), introduction of (wheat) before 1st year of life (99.5% in diabetics compared with 93.0% in controls). Sun exposure was significantly less in cases than in controls (<10 min. /day was 60.0% in diabetics compared with <10 min/day 49.0% in controls, *p*= 0.027) and only 63% of cases received Vitamin D supplementation. There seemed to be a link with the number of vaccinations given, where cases with T1D had had a greater number of extra polio doses above compulsory vaccinations (77.5% in patients compared with 65.0% in controls). Also, exposure to additional vaccines (such as HiB and Rota vaccines) appears to be a possible factor in exposing children to T1D (64.0% in cases compared to 22.5% in controls). **Conclusion:** Environmental risk factors that seemed to have had a possible role in development of T1D in our cases were: early introduction to cow's milk, poor sun exposure and increased number of vaccines in the first 2 years of life. A history of T2D in the family as well as repeated viral infections also played a possible role

Key words:

Type 1 diabetes mellitus, familial, genetics, Vitamin D supplementation, breast feeding, cow milk and vaccines

Contents

List of Abbreviations

ADA	American Diabetes Association
CD	Celiac disease
CSII	Continuous Subcutaneous Insulin Infusion
DEMPU	Diabetes Endocrine and Metabolism Pediatric Unit
DKA	diabetic ketoacidosis
EUR	European
FPG	Fasting plasma glucose
IDDM	Insulin dependent diabetes mellitus
MRNA	messenger RNA
MS	multiple sclerosis
NO2	Nitric dioxide
OGTT	Oral glucose tolerance test
PM10	Particular matter 10
SEA	South-East Asian
SO4	Sulfuric acid
SPSS	Statistical Package of Social Science
T1D	Type1 diabetes
T2D	Type2 diabetes
TH	Thyroid hormone
TSH	thyroid stimulating hormone
UVR	Ultraviolet rays
VIT.D	Vitamin D

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Introduction

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eye, kidney, nerves and blood vessels ***(ADA, 2008).***

Type 1 diabetes is a serious disease that approximately affect 4.9 million people (in all age groups), amounting to 0.09% of the world's population. The number of people with diabetes is expected to increase alarmingly in the coming decades. In 1985 an estimated 30 million people worldwide had diabetes & in 2000 little over a decade later, the figure had risen to over 150 millions. This figure is expected to rise to a type 1 diabetes is one of the most common chronic childhood illnesses, affecting 18 to 20 per 100,000 children a year in the United Kingdom ***(Devendra et al., 2004).***

Affecting approximately 20 million people worldwide ***(Richard, 2004).*** Almost 350 million by 2025 ***(Stern et al., 2005)***.

The incidence of childhood type 1diabetes increased worldwide in the closing decades of the 20th century, but the origins of this increase are poorly documented. Steep rises in the age-group under 5 years have been recorded recently ***(Gale, 2002).***

It seems that two peaks of type1 DM presentation occur in childhood: one before 5 years of age and the other at puberty. The incidence varies with seasonal changes and geography it becomes higher in autumn and winter and lower in the summer ***(Karvonen et al., 2000).***

The prevelance of type 1 diabetes in middle east in children aged 0-14 years old is rising and Egypt is the first country as 25% of patients are in Egypt while in Bahrain is doubled in last 5 years from 25 case /year to 55 case/year .in Kuwait it is 22.3\100000 \year in the same age group, in Pakistan it is less than 1 \1000 00 \year in the same age group

More than a quarter of total some a an annual cases worldwide come from the South-East Asian (SEA) Region and more than a fifth from the European (EUR) Region . Despite having the largest childhood population the Western Pacific (WP) Region has the lowest number of type 1 case ***(IDF, 2003).***

Environmental triggers in infancy and early childhood may accelerate the onset of diabetes. For example, enteroviral infection documented by polymerase chain reaction was detected in twins developing type 1 diabetes in infancy, before detection of islet-cell antibodies ***(Hathout, 2003).***

In recent years, several viruses have been implicated in the pathogenesis of type 1 diabetes. Children with a congenital rubella infection commonly acquire type 1diabetes and children who develop diabetes have experienced more enterovirus infections than control subjects before the appearance of autoantibodies and in fetal life. Single reports have also connected mumps and cytomegalovirus infections with type 1 diabetes ***(Blomqvist et al., 2002).***

According to a Swedish study, children who are exclusively breastfed for a long period of time may be at lower risk of developing type 1 diabetes than those who are not. The researchers also found that postponing new foods and cow's milk seemed to be protective against the development of type 1 diabetes ***(Brekke et al., 2005).***

Another theory is that breastfed children tend to grow more slowly and steadily while formula-fed babies often have growth spurts. That is because mother's milk contains fewer calories than formula ***(Sadauskaite et al., 2004).***

Breast milk protects against enteric infections; enteric infections in turn could increase immunity to dietary antigens by increasing intestinal permeability. It is also possible that an alteration in gut mucosal immune function in genetically susceptible individuals underlies any effect of dietary or viral proteins on the development of islet autoimmunity in early life ***(Couper, 2001).***

Cow's milk feeding is an environmental trigger of immunity to insulin in infancy that may explain the epidemiological link between the risk of type 1 diabetes and early exposure to cow's milk formulas. This immune response to insulin may later be diverted into autoaggressive immunity against beta-cells in some individuals, as indicated by our findings in children with diabetes-associated autoantibodies ***(Vaarala et al, 1999).***

Infantile onset diabetes needs to be distinguished from "Neonatal diabetes" which is a rare entity. In the majority of such cases, however diabetes disappears within few weeks to few months and this condition is termed as "Transient Diabetes Mellitus of New Born" or "Transient Neonatal Diabetes Mellitus". Very few of these cases continue to have permanent diabetes whereas onset of diabetes after one month of age i.e. infantile onset diabetes is likely to be permanent and therefore termed as Permanent Diabetes Mellitus of Infancy ***(Kumar, 2002).***

Aim of the Work

To study possible non genetic risk factors that might have caused T1D in a group of infants and toddlers (6 months to 2 years of age) presenting to the Diabetes, Endocrine, Metabolic, Pediatric Unit (DEMPU) of Cairo University Children's Hospital.

Diabetes Mellitus Type-1

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemic resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association, 2011).***

Type 1 DM is the most common metabolic disease of childhood. About 1 in every 400-600 children and adolescents has type 1 DM. In adults, type 1 DM constitutes approximately 5% of all diagnosed cases of diabetes ***(Patino et al., 2010).***

Pathophysiology

Insulin is essential to process carbohydrates, fat, and protein. Insulin reduces blood glucose levels by allowing glucose to enter muscle cells and by stimulating the conversion of glucose to glycogen (glycogenesis) as a carbohydrate store. Insulin also inhibits the release of stored glucose from liver glycogen (glycogenolysis) and slows the breakdown of fat to triglycerides, free fatty acids, and ketones. It also stimulates fat storage. Additionally, insulin inhibits the breakdown of protein and fat for glucose production (gluconeogenesis) in both liver and kidneys ***(Nainggolan, 2013).***

Hyperglycemia (i.e., random blood glucose concentration more than 200 mg/dL or 11 mmol/L) results when insulin deficiency leads to uninhibited gluconeogenesis and prevents the use and storage of circulating glucose ***(Rosenbloom et al., 2009).***

The kidneys cannot reabsorb the excess glucose load, causing glycosuria, osmotic diuresis, thirst, and dehydration. Increased fat and protein breakdown leads to ketone production and weight loss. Without insulin, a child with type 1 diabetes mellitus wastes away and eventually dies due to diabetic ketoacidosis (DKA) ***(Porter et al., 2004).*** An excess of insulin prevents the release of glucose into the circulation and results in hypoglycemia (blood glucose concentrations of <60 mg/dL or 3.5 mmol/L). Glucose is the sole energy source for erythrocytes, kidney medulla, and the brain ***(Barrett, 2007).***

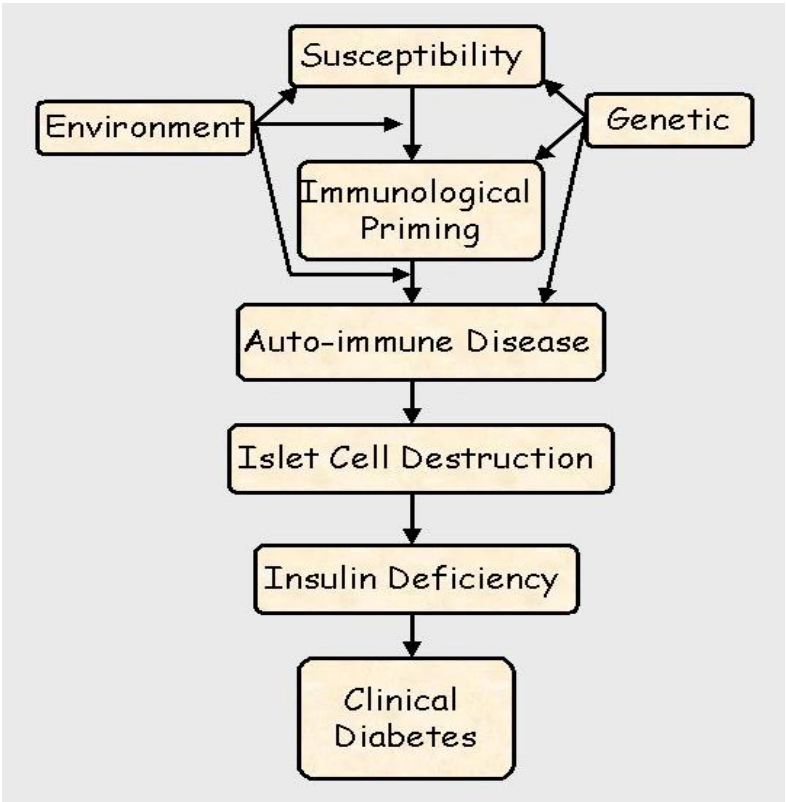

Fig. (1): Possible mechanism for development of type 1 diabetes (Hattersley et al., 2009)

Signs and symptoms

Main symptoms of type 1 diabetes a polyuria, polydipsia, polyphagia, and unexplained weight loss. Other symptoms may include fatigue, nausea, and blurred vision.

The onset of symptomatic disease may be sudden. It is not unusual for patients with type 1 diabetes to present with diabetic ketoacidosis (DKA) ***(Clarke et al., 2009).***

Diagnosis

Diagnostic criteria by the American Diabetes Association (ADA) include the following:

- A fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L), or
- A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), or
- A random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis ***(Nainggolan, 2013).***

Screening

Screening for type 1 diabetes in asymptomatic low-risk individuals is not recommended. However, in patients at high risk (e.g., those who have first-degree relatives with type 1 diabetes), it may be appropriate to perform annual screening for anti-islet antibodies before the age of 10 years, along with 1 additional screening during adolescence ***(Vehik et al., 2011).***