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Timing, Bonding, And Trauma:

Applications from Experience-Dependent Maturation and Traumatic Stress Provide Insights for Understanding Environmental Origins of Disease

by

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Excerpt pp 28-32: Risk Factors for Type 1 Diabetes Before, During and After Birth

Dear Readers,

This is an excerpt from a book chapter I wrote for Nova Science publishers about risk factors for type 1 diabetes in 2007. This particular section presents studies showing increased risk from stressful events in pregnancy, birth and infancy. Much more research has emerged since then that further supports these findings, and I write about this on my chronic illness blog. Other sections of the chapter describe the science explaining how such factors have been found to affect the developing brain, immune system, gut and other biological functions and more. There are also sections on similar risk factors for asthma and inflammatory bowel disease (IBD). Email me for a copy of the entire chapter.

Sincerely,
Veronique

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Type 1 Diabetes

INTRODUCTION

Environmental factors are believed to account for more than 50% of risk for type 1 diabetes (T1D) [133, 134]. T1D demonstrates tremendous variability in populations of similar genetic and cultural backgrounds, can occur in clusters and epidemics, and varies tremendously by geographic location [135]. Incidence rates vary by a factor of 350 worldwide, with differences in Europe alone varying by a factor of 50 between Macedonia, which has the lowest incidence, and Finland [136], which has the highest incidence rates in Europe and in the world [135]. Incidence of T1D has been increasing since World War II [137, 138], and in some areas this increase appears to be due to a shift to a younger age of onset [139]. An understanding of the relationship between these numerous and seemingly unrelated environmental factors has been difficult to elucidate. Theories presented in section I appear to provide a synthesizing perspective for explaining the complex relationship between risk factors for this disease [140, 141]. Of the group at high genetic risk, 90% of people who are newly diagnosed have no close relatives with T1D, and only 10% [136] will ever develop the disease [142].

T1D appears to have been studied in the most depth regarding the role of initiating and precipitating environmental events in early life. Factors making this a particularly appropriate disease for the evaluation of environmental factors are numerous, and include the fact that T1D 1) is one of the most common diseases in childhood, 2) has a well-identified period of onset in early childhood and adolescence with diagnosis occurring prior to age 21 in 75% of cases [143], 3) is associated with identifiable genetic markers in most individuals, and 4) has clearly identifiable diagnostic signs and symptoms. T1D is also commonly associated with autoantibodies, which are predictive of risk and often detectable for years prior to diagnosis. All of these factors facilitate the use of population-based studies and prospective research designs beginning early in life.

Epidemiology and Patterns of Evolution

T1D has been hypothesized to require three elements in order for clinically evident disease to arise. These elements include genetic susceptibility with initiation by exposure to an exogenous trigger during a critical time in life followed by high subsequent exposure to an antigen that drives beta cell destruction (see Figure 10) [136]. Without all of these components, it is predicted that T1D will not occur. This hypothesis would help to account for the minority of individuals at genetic risk who never develop the disease [136].

Stressful events have been proposed to be important environmental factors that accelerate the loss of beta cell function through multiple events or “hits” [144] and to eventually precipitate or unmask the disease [137, 145-147]. T1D develops following a prodrome of variable duration, during which diabetes-related autoantibodies develop and beta cell destruction occurs.

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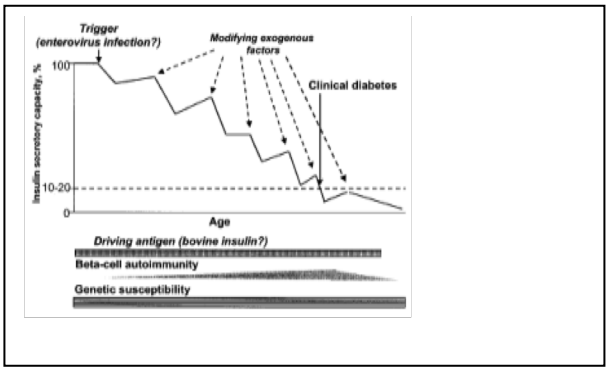

Figure 10. Progression from genetic susceptibility to overt type 1 diabetes.

> "According to this model, the disease process is triggered by an exogenous factor, driven by another environmental determinant, and modified by a series of environmental factors in individuals with increased genetic disease susceptibility." p. S127 in Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Copyright © 2005 American Diabetes Association. From Diabetes, Vol. 54, 2005; S125-S136 Reprinted with permission from The American Diabetes Association.

Patterns of Autoimmunity

Risk for T1D is associated with the presence of autoantibodies to islet cells (ICA), insulin (IAA), and glutamate acid decarboxylase (GAD or GAA) [143] even though none of these antibodies are specific for beta cells [146, 148]. The presence of one antibody is common in the general population [136], and only a small number of individuals with autoantibodies progress to type 1 diabetes [149, 150]. In fact, these antibodies remit in up to 78% of individuals, perhaps due to decreased exposure to the triggering factor [147].

Antibody levels fluctuate [147] and exhibit transiency [151, 152], and risk for T1D rises with increasing level [153], persistence [151], sequential progression [154], and presence of multiple antibodies [150, 155]. The incidence of autoantibodies appears to decrease with age [147] and conversion to autoantibody positivity is rare over the age of 10 [143, 144, 147]. Diabetic twins tend to have higher levels of antibodies than their nondiabetic co-twins, which cannot be accounted for by genetic factors alone [153]. Furthermore, when one twin develops diabetes, the co-twin usually follows within 5 years, after which risk decreases [153].

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RISK FACTORS BEFORE, DURING AND AFTER BIRTH

Important environmental risk factors for type 1 diabetes appear to originate during a limited period of exposure [133, 156] in early life [134-136, 146, 157-160] and are proposed to be factors to which only children are exposed [156]. Environmental factors are believed to affect risk during prenatal life [133, 134, 137-139, 156, 158, 161-164], and this hypothesis appears to be supported by the recent finding that diabetes-related antibodies have been identified at birth in infants of nondiabetic mothers [165].

Prenatal Risk Factors

Prenatal risk factors associated with increased risk for T1D include maternal infection [137, 162, 166], placenta previa [167] and nonspecific pregnancy complications [168]. Prenatal procedures such as amniocentesis have also been associated with risk although the reasons for the procedure, such as concern for the baby or older maternal age, were not described [164]. The process of amniocentesis can be a stressful experience for both mother and infant [169].

Common factors linking perinatal factors associated with risk for T1D appear to be that they are stressful [170] and increase risk for maternal-infant bonding disruptions through exposure to events such as medical illness, pain, stress, and/or early separation. Some early risk factors, such as preeclampsia and blood group incompatability, also involve states of altered maternal physiological regulation.

Preeclampsia

Preeclampsia is associated with increased risk for T1D in most [159, 164, 170, 171], although not all [160] studies. Any exposure to preeclampsia has been found to reduce the age of onset to under 15 years of age [170], and exposure in the first or second trimester increases risk for T1D [164].

Preeclampsia represents a state of increased maternal sympathetic activity [172-176] and can be life-threatening to both mother and fetus. As presented earlier, exposure to maternal states of altered regulation during critical periods can predispose the growing child to disease [177]. Preeclampsia has been associated with increased blood pressure in 12-year-old children and the impact of preeclampsia on children who were small for gestational age is even larger, with associated changes in cortisol levels [178].

Maternal-Child Blood Group Incompatibility

Maternal-child blood group incompatibility has been associated with T1D in the Swedish Childhood Diabetes Study [159, 170], and increased severity requiring phototherapy, which is a procedure that separates mother and infant for the treatment of infant jaundice, is associated with greater risk for onset before 5 years of age. Blood group incompatability was not associated with risk for T1D in one study [179] or for antibody development in another [180].

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Labor and Delivery Complications

Increased risk for T1D has also been associated with labor complications [164] and oxytocin [167], which is a medication generally used to facilitate uterine contractions to initiate or facilitate labor. Assisted delivery involving forceps, vacuum, and breech extractions has been associated with increased risk for the development of autoantibodies and T1D [180]. Cesarean deliveries, which are associated with risk in many [160, 164, 170] but not all [159, 167, 180-182] studies, have been found to increase risk for onset prior to 15 years of age [170]. Risk also varies by the type of cesarean, and higher risk has been associated with elective cesareans in one study [160] and with emergency sections with near statistical significance in another [164].

Size and Gestational Age at Birth

Size and gestational age at birth show conflicting results. An increased risk for T1D has been associated with smaller birth weight [159], as well as *s*hort [170] and prolonged gestation [168]. In another study, poor intrauterine growth and small size for gestational age decreased risk. Risk increased with large size for gestational age and with increasing birth weight in mothers who do not have type 2 diabetes, as well as with excess growth postpartum [183, 184]. High birth weight has been found to be associated with risk only in children who develop the disease before 10 years of age in one study [184] and risk for T1D within a limited window may explain why most studies find no association with birth weight [160, 163, 182, 185] or gestational age [160, 163, 164, 182, 183, 186]. Given that T1D is higher when a parent has type 2 diabetes and that birth weights are higher in babies born to mothers who have diabetes during pregnancy [187], it is also interesting to speculate that increasing risk with higher birth weights could reflect exposure to subclinical states of maternal physiological dysregulation.

Rapid growth in infancy is associated with increased risk for T1D, and may at least in part precipitate onset due to an increased demand on insulin production [188]. As we have seen, timing of prenatal stress can increase risk for smaller birth size and shorter gestational length and can also affect the baby's HPA axis. Since the baby appears to play an important role in initiating labor [189], contradictory findings regarding risk with gestational age may reflect variability in prenatal patterns of fetal regulation. Cascading effects may be further compounded by growth-related demands on insulin to facilitate progression to diabetes.

Neonatal Events

Increased risk for T1D is associated with neonatal events such as the need for postpartum intensive care [168], as well as infection and respiratory difficulties associated with fetal distress, such as birth asphyxia [164] and respiratory disease [159, 170]. Low APGARS (< 6 at 5 minutes) were not associated with risk in the one study known to have assessed impact [170].

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Postpartum Events

Jaundice

Jaundice is associated with increased risk for T1D regardless of association with maternal blood group incompatability [190], and greater severity requiring phototherapy further augments risk [170]. In an exploratory study in mice predisposed to risk for T1D-related disease, maternal-infant separation, rather than the treatment of phototherapy per se, was the factor identified with risk for diabetes [170]. These findings suggest a role for bonding disruptions, traumatic stress, and loss of psychobiological regulation in risk for T1D.

Breastfeeding

Exclusive breastfeeding, even when only measured at postpartum hospital discharge [164], has been associated with a decreased risk for T1D, and duration of exclusive breastfeeding for more than 4 months is associated with decreased risk of autoantibody positivity in genetically at-risk individuals [191]. Earlier onset of weaning [179], as well as lack [163, 192-194] and shorter duration [179, 186, 194, 195] of breastfeeding are also more likely in individuals with T1D than in controls. Shorter duration of breastfeeding is also associated with increased risk of autoantibody development [191], perhaps due to the early introduction of cow's milk and other foods, although this is not the finding in every at-risk study population [196, 197]. Interestingly, a few studies have found that longer duration of breastfeeding is associated with trends [197, 198] as well as statistically significant increases [199] in T1D. The study authors [199] suggest that the small number of study participants may account for this finding as may the fact that risk of ever breastfeeding was not evaluated.

Formula feeding with soy products has been associated with higher risk of T1D as well as the development of thyroid antibodies [200], which are common in T1D [142]. The early introduction of supplementary milk [168] such as cow's milk formula before 3 [179, 188, 201] and 4 [191] months of age is also associated with increased risk for seroconversion to antibody positivity [191, 201] as well as T1D [179, 188], although use of cow's milk is not associated with risk in all studies [198, 202].

Incidence of T1D has been found to fluctuate with variations in breastfeeding patterns in Scandinavian populations of similar genetic makeup [193] and breastfeeding is proposed to be protective [193, 194], whether by enhancing the infant's immune response [194], reducing the number [193] or severity of early infections [203], or by delaying the early introduction of other foods [194]. Because breastfeeding facilitates slower growth, it has also been proposed to reduce risk because higher weight gain early in life is associated with increased risk for T1D [188]. Another possible role of early feeding practices is the finding that bottle feeding and nonexclusive breastfeeding are associated with greater infant sympathetic nervous system reactivity to stress than exclusive breastfeeding [204], suggesting that breastfeeding may be protective or delay onset, whereas bottle feeding may increase or perhaps even contribute to initiating risk.

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