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Infections- one cause, among others, of Type 1 diabetes

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ABSTRACT

The etiology of Type 1 diabetes (T1D) is unknown. Infections may play a role. Several types and species of virus have been connected to development of T1D. Thus not only enterovirus like Coxsackie or Echovirus may be involved but also several others eg mumps, rotavirus, CMV, Parecho-virus, Ljungan-virus, EB-virus . Virus may have different roles depending on when in relation to the diabetes development the infection occurs. Very early in life, perhaps already during fetal life, virus may damage beta cells and/or influence the immune system, and start an autoimmune process. Infections years later may stimulate the disease process or finally precipitate the manifest disease. Although clinical pancreatitis is a rare cause of T1D bacterial infections could also be involved. Furthermore, beside the typical infectious damaging beta cells and/or influencing the immune system, infections lead to increased insulin demand with beta cell stress and may therefore play similar role as any other factor causing beta cell stress like growth, puberty, psychological stress. Prevention or cure of infections playing a role for development of T1D needs to be tried but will have to be of various kinds, and given at different time-points. Efficacy in some patients is better than no efficacy at all.

Different Types of Infections

The etiology of Type 1 diabetes (T1D) is unknown [1]. One main hypothesis is that the disease is caused by a virus. It was noted early that mumps now and then lead to a pancreatitis, which could be followed by T1D [2], and we and others showed that mumps infection of pancreas could be followed by autoantibodies against the beta cells of the islets [3,4]. In the end of 1960:es epidemiological studies again gave new life to the virus hypothesis [5] and especially Coxsackie-virus were suspected . Then when Yoon and Notkins described their famous case [6] when Coxsackie-virus could be isolated from pancreas of a boy who died acutely in diabetic keto-acidosis and then shown to cause autoimmune diabetes in experimental animal, the riddle seemed to be solved. Coxsackie-virus cause T1D, and the question is if it is THE cause of the disease or not. Since then the research on virus and Type 1 diabetes has grown and in recent years ca 700 scientific papers have been published per year, but with limited result. Infections during pregnancy seem to be related to increased risk of T1D in the child, but these infections thought to be enterovirus infections, perhaps especially gastrointestinal [7,8] seem at least as often to be upper respiratory infections [9] and it is unclear in what way these infections influence the beta cells of pancreas, or play their role by influencing the immune system. Furthermore, as well as eg meningitis can be caused by a number of viruses and bacteria, it is natural that pancreatitis, general or more restricted to islets, can be caused by a number of infectious agents. Thus, several different viruses such as EB-virus, CMV-virus, Ljunganvirus have been associated to autoimmune diabetes [10-13] and pancreatitis can also be caused by bacteria [14].

Different Times and Mechanisms of Infections

Different possible agents is one problem for selection of effective treatment. Another big problem is to decide when the treatment should be given. Infections may cause their damage very early in life eg during fetal life, or first year of life, thereby either killing enough beta cells or starting an autoimmune reaction in genetically predisposed individuals. We have so far no good markers indicating when antiviral or antibacterial treatment should be instituted. Vaccinations against certain suspected virus strains could be one way of finding evidence of the importance of a virus or group of viruses. The vaccinations against mumps virus certainly

eradicated mumps, but there was no change of the incidence curve in countries like Sweden when that vaccination became general for all children. In recent years rotavirus vaccination has become part of the vaccination program in certain countries. In Australia one speculates whether there was a drop in incidence related to that new vaccination [15] while nothing was seen in Finland when the vaccination was introduced [16]. Now there is ongoing work to produce vaccine against enterovirus.

Such vaccination early in life can hopefully prevent at least some cases of T1D. Prevention of a small percentage is better than no prevention at all!With irregular intervals during childhood infections could instead, or also, cause a new damage with repeated attacks by different species, or finally attack close to the clinical manifestation of T1D. Studies have shown increased amount of antibodies against certain infections in connection with diagnosis of manifest diabetes [17], and infections early before diagnosis has been found to be related to a more rapid decline of beta cell function [18]. These mechanisms may differ depending on age of the patient, gender, geographical region, genetic background. In biopsies from 6 newly-diagnosed adult Type 1 diabetic patients, as part of the DiViD-trial, there may exist virus in islets, but the virus population seems to be extremely small (1 dot in 2000 islet cells among 1-2% of islets!) [19]. Whether this finding is a proof of persistent virus infection or means nothing for the disease process is impossible to say. The DiViDInt study (antiviral treatment with Ribavirin and Pleconaril) may tell if antiviral treatment at diagnosis of T1D is meaningful leading to preservation of beta cell function for some year/s after the end of the treatment. Antiviral treatment, as well as antibacterial treatment, should reasonably in any case cure some ordinary infections, which then may lead to less beta cell stress, better blood glucose balance and transient preservation of beta cell function , even when these agents have no causal role for the diabetes process.

Infections Cause Beta Cell Stress

Infections may play a role for development of T1D in other ways then via direct attack on beta cells or influencing the immune system. T1D has its peak of incidence during puberty, which strongly suggests that the disease becomes manifest when the increasing insulin demand becomes greater than the residual insulin secretion. This illustrates how increasing beta cell demand can at least precipitate manifest diabetes, and it is shown in different studies that eg rapid growth [20], psychological stress [21], and increasing BMI [22] is associated with development of T1D. Infections are wars for the body when the demand for insulin increases, and therefore infections may well accelerate the process and sometimes precipitate manifest diabetes even when the infection does not hurt the beta cells or influence the immune system. Unfortunately even the most efficient support of the beta cells with beta cell rest only delays the disease process and may preserve the beta cell function for some time [23,24], which means that there is a damaging process ongoing. The beta cell stress may have caused oxidative stress with abnormal proteins attracting the immune system to react [25], or the increased antigen release per se [26], in similar ways as when a damaging agent eg a virus has killed beta cells with increased antigen release, may cause an autoimmune reaction.

Conclusion

Infections play different roles for development of T1D. Interventions have to be of various kinds as different infectious agents and different mechanisms at different stages are involved in the T1D development.

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