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November 2012

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Diabetes Mellitus Type 1

Main article: Diabetes mellitus

Diabetes mellitus type 1 (Type 1 diabetes, IDDM, or juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas.[2] The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss result.[3]

Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaled insulin has been available at various times. Pancreas transplants have been used to treat type 1 diabetes; however, this procedure is currently still at the experimental trial stage.[4]

There is no preventive measure against developing type 1 diabetes. Most people who develop type 1 are otherwise healthy.[5] Although the cause of type 1 diabetes is still not fully understood it is believed to be of immunological origin. Type 1 can be distinguished from type 2 diabetes via a C-peptide assay, which measures endogenous insulin production.

Type 1 treatment must be continued indefinitely in all cases. Treatment need not significantly impair normal activities, if sufficient patient training, awareness, appropriate care, discipline in testing and dosing of insulin is taken. However, treatment is burdensome for many people. Complications may be associated with both low blood sugar and high blood sugar. Low blood sugar may lead to seizures or episodes of unconsciousness and requires emergency treatment. High blood sugar may lead to increased tiredness and can also result in long term damage to other organs such as eyes and joints.

Signs and symptoms

The classical symptoms of type 1 diabetes include: polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss.[6]

Cause

Environment

Environmental factors can strongly influence expression of type 1. A study showed that for identical twins, when one twin had type 1 diabetes, the other twin only had type 1 30%–50% of the time. Despite having the exact same genome, one twin had the disease, where the other did not; this suggests that environmental factors, in addition to genetic factors, can influence disease prevalence.[7]

Genetics

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its expression. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between. The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21. This is believed to be responsible for the histocompatibility disorder characteristic of type 1: Insulin-producing pancreas cells (beta cells) display improper

antigens to T cells. This eventually leads to the production of antibodies that attack these beta cells. Weaker genes are also located on chromosomes 11 and 18.

Pathophysiology

The cause of type 1 diabetes is not fully understood. Some theorize that type 1 diabetes is a virally triggered autoimmune response in which the immune system attacks virus infected cells along with the beta cells in the pancreas. The Coxsackie virus family or German measles is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the Islets of Langerhans are destroyed decreasing endogenous insulin production. This distinguishes type 1's origin from type 2 DM. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

This vulnerability is not shared by everyone, for not everyone infected by the suspected organisms develops type 1 diabetes. This has suggested presence of a genetic vulnerability [8] and there is indeed an observed inherited tendency to develop type 1. It has been traced to particular HLA genotypes, though the connection between them and the triggering of an auto-immune reaction is still poorly understood.
Short breast-feeding period and short attendance to day care is associated with the risk of type 1 diabetes in Czech children. [9]

Some researchers believe that the autoimmune response is influenced by antibodies against cow's milk proteins. [10]

No connection has been established between autoantibodies, antibodies to cow's milk proteins, and type 1 diabetes. A subtype of type 1 (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with type 2. In addition, a small proportion of type 2 cases manifest a genetic form of the disease called maturity onset diabetes of the young (MODY).

Vitamin D in doses of 2000 IU per day given during the first year of a child's life has been connected in one study in Northern Finland (where intrinsic production of Vitamin D is low due to low natural light levels) with an 80% reduction in the risk of getting type 1 diabetes later in life. The causal connection, if any, is obscure.

Type 1 diabetes was previously known as juvenile diabetes because it is one of the most frequent chronic diseases in children; however, the majority of new-onset type 1 diabetes is seen in adults. Scientific studies that use antibody testing (glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), and insulinoma-associated (IA-2) autoantibodies) to distinguish between type 1 and type 2 diabetes demonstrate that most new-onset type 1 diabetes is seen in adults. A 2008 book, “Type 1 Diabetes in Adults: Principles and Practice” (Informa Healthcare, 2008) says that adult-onset type 1 autoimmune diabetes is two to three times more common than classic childhood-onset autoimmune diabetes (p. 27). In type 1 diabetes, the body does not produce insulin. Insulin is a hormone that is needed to convert sugar (glucose), starches and other food into energy needed for daily life.

Some chemicals and drugs preferentially destroy pancreatic cells. Pyrinuron (Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental or intentional ingestion. Vacor was withdrawn from the U.S. market in 1979, but is still used in some countries. Zanosar is the trade name for streptozotocin, an antibiotic and antineoplastic agent used in chemotherapy for pancreatic cancer; it also kills beta cells, resulting in loss of insulin production. Other pancreatic

problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin production.

The exact cause(s) of type 1 diabetes are not yet fully understood, and research on those mentioned, and others, continues.

Diagnosis

Management

Main article: Diabetes management

Type 1 is treated with insulin replacement therapy—usually by insulin injection or insulin pump, along with attention to dietary management, typically including carbohydrate tracking, and careful monitoring of blood glucose levels using glucose meters. Today the most common insulins are biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish. Major global suppliers include Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis. A more recent trend, from several suppliers, is insulin analogs which are slightly modified insulins which have different onset of action times or duration of action times.

Untreated type 1 diabetes commonly leads to coma, often from diabetic ketoacidosis, which is fatal if untreated. Continuous glucose monitors have been developed and marketed which can alert patients to the presence of dangerously high or low blood sugar levels, but technical limitations have limited the impact these devices have had on clinical practice so far.

In more extreme cases, a pancreas transplant can restore proper glucose regulation. However, the surgery and accompanying immunosuppression required is considered by many physicians to be more dangerous than continued insulin replacement therapy, and is therefore often used only as a last resort (such as when a kidney must also be transplanted, or in cases where the patient's blood glucose levels are extremely volatile). Experimental replacement of beta cells (by transplant or from stem cells) is being investigated in several research programs. Thus far, beta cell replacement has only been performed on patients over age 18, and with tantalizing successes amidst nearly universal failure.

Pancreas transplantation

Main article: Pancreas transplantation

Pancreas transplants are generally performed together with or some time after a kidney transplant. One reason for this is that introducing a new kidney requires taking immunosuppressive drugs such as cyclosporin. Nevertheless this allows the introduction of a new, functioning pancreas to a patient with diabetes without any additional immunosuppressive therapy. However, pancreas transplants alone can be wise in patients with extremely labile type 1 diabetes mellitus.[12]

Islet cell transplantation

Main article: Islet cell transplantation

Islet cell transplantation is expected to be less invasive than a pancreas transplant which is currently the most commonly used approach in humans.

In one variant of this procedure, islet cells are injected into the patient's liver, where they take up residence and begin to produce insulin. The liver is expected to be the most reasonable choice because it is more accessible than the pancreas, and islet cells seem to produce insulin well in that environment. The patient's body, however, will treat the new cells just as it would any other introduction of foreign tissue, unless a method is developed to produce them from the patient's own stem cells or there is an identical twin available who can donate stem cells. The immune system will attack the cells as it would a bacterial infection or a skin graft. Thus, patients now also need to undergo treatment involving immunosuppressants, which reduce immune system activity.

Recent studies have shown that islet cell transplants have progressed to the point that 58% of the patients in one study were insulin independent one year after islet cell transplant.[13] Ideally, it would be best to use islet cells which will not provoke this immune reaction. Scientists in New Zealand with Living Cell Technologies are currently in human trials with Diabecell, placing pig islets within a protective capsule derived of seaweed which enables insulin to flow out and nutrients to flow in while protecting the islets from immune system attack via white blood cells.

Prognosis

Complications of poorly-managed type 1 diabetes mellitus may include cardiovascular disease, diabetic neuropathy, diabetic retinopathy among others. Overweight or obese people having T1DM are especially likely to have these problems if substandard diet is involved or the cholesterol or blood pressure is not well-controlled.[14] There is some evidence that cardiovascular disease[15] as well as neuropathy[16] may, in fact, have an autoimmune basis as well.

Epidemiology

It is estimated that about 5%–10% of North American diabetes patients have type 1. The fraction of type 1 in other parts of the world differs; this is likely due to both differences in the rate of type 1 and differences in the rate of other types, most prominently type 2. Most of this difference is not currently understood. Variable criteria for categorizing diabetes types may play a part. The longest surviving Type I diabetes patient is Gladys Dull, who has lived with the condition for over 83 years.

Research

This section is an incomplete list of mainly commercial companies but also other entities, namely governmental institutions and individual persons, actively involved in research towards finding a cure to diabetes type 1. It does not list research funds, hospitals in which research is undertaken, etc., but only the industrious, actual developers of such products.

Entities are listed alphabetically along with their status of research in that field, so that also entities which ceased research into finding a cure to diabetes type 1 may be listed.

Amylin Pharmaceuticals – is working toward finding a cure, and has a drug on the market called Symlin (pramlintide acetate) that helps in treating type 1 diabetes

Cerco Medical [1] – Present status: Unknown

Denise Faustman [2] – Present status: Working on immune modification

DeveloGen [3] – Present status: Developing DiaPep 277

Diamyd Medical [4] – Present status: Developing GAD65-based vaccine (phase III trial started)

Tolerx, Inc. [www.defendagainstdiabetes.com] - Present status: Now (4/2009) in Phase 3 clinical study of otelixizumab, an Fc-disabled, anti-CD3 monoclonal antibody in patients with new onset (diagnosis within last 10 weeks) type 1 diabetes.

National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases http://t1dstudy.niddk.nih.gov/about.html

Living cell technologies, Diabecell: http://www.lctglobal.com/lct-diabecell-diabetes-treatment.php

Research foundations

The Juvenile Diabetes Research Foundation (JDRF) is the major charitable organization in the USA, Canada and Australia devoted to type 1 diabetes research. JDRF's mission is to cure type 1 diabetes and its complications through the support of research. Since its founding in 1970, JDRF has contributed more than $1.3 billion to diabetes research, including more than $156 million in FY 2008. In FY 2008, the Foundation funded 1,000 centers, grants and fellowships in 22 countries. In November 2008 JDRF launched a new online social network for people with type 1 diabetes--*Juvenation.

The International Diabetes Federation is a worldwide alliance of over 160 countries to address diabetes research and treatment. The American Diabetes Association funds some work on type 1 but devotes much of its resources to type 2 diabetes due to the increasing prevalence of the type 2 version. Diabetes Australia is involved in promoting research and education in Australia on both type 1 and type 2 diabetes, however, like the American Diabetes Association, spends most of its time and resources on type 2. The Canadian Diabetes Association is also involved in educating, researching, and sustaining sufferers of type 1 Diabetics in Canada. Pacific Northwest Diabetes Research Institute conducts clinical and basic research on type 1 and type 2 diabetes.

Prevention

"Immunization" approach

If a biochemical mechanism can be found that prevents the immune system from attacking beta cells, it may be administered to prevent commencement of diabetes type 1. Several groups are trying to achieve this by causing the activation state of the immune system to change from Th1 state (“attack” by killer T Cells) to Th2 state (development of new antibodies). This Th1-Th2 shift occurs via a change in the type of cytokine signaling molecules being released by regulatory T-cells. Instead of pro-inflammatory cytokines, the regulatory T-cells begin to release cytokines that inhibit inflammation.[17] This phenomenon is commonly known as "acquired immune tolerance".

DiaPep277

A substance designed to cause lymphocyte cells to cease attacking beta cells, DiaPep277 is a peptide fragment of a larger protein called HSP60. Given as a subcutaneous injection, its mechanism of action involves a Th1-Th2 shift. Clinical success has been demonstrated in prolonging the "honeymoon period" for people who already have type 1 diabetes.[18] The product is currently being tested in people with latent autoimmune diabetes of adults (LADA).

Ownership of the drug has changed hands several times over the last decade. In 2007, Clal Biotechnology Industries (CBI) Ltd., an Israeli investment group in the field of life sciences, announced that Andromeda Biotech Ltd., a wholly

owned subsidiary of CBI, signed a Term Sheet with Teva Pharmaceutical Industries Ltd. to develop and commercialize DiaPep277.[19]

Intra-nasal insulin

There is pre-clinical evidence that a Th1-Th2 shift can be induced by administration of insulin directly onto the immune tissue in the nasal cavity. This observation has led to a clinical trial, called INIT II, which began in late 2006, based in Australia and New Zealand.

BCG research

Tumor necrosis factor-alpha, or TNF-α, is part of the immune system. It helps the immune system distinguish self from non-self tissue. People with type 1 diabetes are deficient in this substance. Dr. Denise Faustman theorizes that giving Bacillus Calmette-Guérin (BCG), an inexpensive generic drug, would have the same impact as injecting diabetic mice with Freund's Adjuvant, which stimulates TNF-α production. TNF-α kills the white blood cells responsible for destroying beta cells, and thus prevents, or reverses diabetes.[20] She has reversed diabetes in laboratory mice with this technique, but was only able to receive funding for subsequent research from The Iaccoca Foundation, founded by Lee Iacocca in honor of his late wife, who died from diabetes complications. Human trials are set to begin in 2008.

Diamyd

Diamyd is the name of a vaccine being developed by Diamyd Medical. Injections with GAD65, an autoantigen involved in type 1 diabetes, has in clinical trials delayed the destruction of beta cells for at least 30 months, without serious adverse effects. Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells.[21] Phase III trials are under way in the USA [22] and in Europe, with most sites actively pursuing participants.[23][24][25] Two prevention studies, where the vaccine is given to persons who have not yet developed diabetes, will start in 2009[26][27].

See also

Kara Neumann case – "treatment" by prayers case resulting in death

Further reading

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) - Diabetes in America Textbook (PDFs)

Juvenile Diabetes Research Foundation - What is type 1 diabetes

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25. ^ Diamyd Announces Completion of type 1 Diabetes Vaccine Trial with Long Term Efficcacy Demonstrated at 30 Months
26. ^ MSNBC News: Pioneering Diamyd(r) Study to Prevent Childhood Diabetes Approved
27. ^ Diamyd press release: Diamyd approved for groundbreking study in Norway

External links

IDF Diabetes Atlas

International Diabetes Federation

Juvenile Diabetes Research Foundation International

Juvenile Diabetes Research Foundation - Canada

Juvenile Diabetes Research Foundation - Australia

Type 1 Diabetes Blog

Beta Cell Biology Consortium - Team science with the aim of developing a cell-based therapy for type 1 diabetes

Summary of Current Research in Type-1 Diabetes Cures

Diabetes Section of The Hormone Foundation

Juvenation a social network for people with type 1 diabetes created by the Juvenile Diabetes Research Foundation

Online Diabetes Support Team at the Juvenile Diabetes Research Foundation

Children with Diabetes

Young Diabetics

type 1 Diabetes TrialNet

type 1 Diabetes at the American Diabetes Association

National Diabetes Information Clearinghouse

World Diabetes Day

Math models of a Type-1 diabetic for artificial pancreas design