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Type I Diabetes

Tuesday, February 19, 2008
9:00 AM

- Diabetes Mellitus: systemic disease with multiple metabolic abnormalities, mainly elevation in plasma glucose (lipid metabolism, ketones)
- Classification
 - Type I
 - A. Immune Mediated - 85%
 - B. Idiopathic - 15%
 - Type II
 - Other types (MODY, secondary DM)
- Signs of Type I: Polyuria; Polydipsia (thirst); Polyphagia (hunger); weight loss; fatigue; increased frequency of infections; rapid onset (type II is much slower progressing); insulin dependent; early onset
- Differences btwn type I and II: type I has islet cell antibodies and patients are typically thin
 - HLA related genetic background, no insulin secretion, non-insulin resistant, non-responsive to oral meds, ketosis prone
 - Type I is only 5% (1.5-2mm cases)
- Type I is chronic autoimmune disease but can also develop in adults/elderly
 - Polygenic: HLA linkage, non-MHC genes
 - Autoimmune etiology: antibodies to islet autoantigens, autoreactive T cells
 - Immune modulation alters course: antigen vaccination, general immunosuppression
- Graph on pg. 297
 - Will see multiple antibodies during beta cell injury phase
 - Declining beta cell mass
 - Loss of first phase insulin response (pre-diabetes)
 - Diabetes full blown once mass is below 10%
- Type I
 - Insulin resistance
 - β cell hypertrophy
 - Islet inflammation, pathogenic T cells, β cell decomposition
 - Impaired glucose tolerance
 - Autoimmune diabetes, insulinitis, β cell death
- Genetic Links
 - Lifetime empiric risk increases w/ close relatives
 - Father has greater effect than mother --> imprinting
 - HLA class II genes have highest incidence
 - HLA complex: (DQ2, DQ8), DR3, DR4 are most associated w/ Type I
 - Sibling sharing 2 HLA haplotypes w/ type I affected sibling at much higher risk of developing
- Multiple factors
 - Autoreactive T cells --> islet autoantibodies (not shown to directly kill β cells)
 - Elevated cytokines (IFN γ , IL-1 β , TNF α , etc.)
 - Increased apoptosis/necrosis, decreased neogenesis
 - Hyperglycemia --> glucose toxicity
 - Environmental Factors
 - All combine to lead to β cell death
- Environmental factors
 - Congenital rubella syndrome - similar antigens to those in Type I DM --> immune response
 - Cocksakie B virus?
 - Enterovirus?
 - Streptozotocine (low doses)?
- Loss of self tolerance to self-antigens

- Insulin - main antigen in T1DM
- GAD65
- ICA512/IA-2
- Znt8 - 60% of Type I
- Can be one or multiple antigens
 - Starts w/ insulin --> epitope spreading to GAD, Znt8, IA2
- Theory is that not enough insulin enters thymus during T cell development --> recognition as non-self
- T Cells
 - Cell-mediated immunity
 - CD4
 - CD8
 - NK cells?
 - M'phages?
 - Dendritic cells?
 - Normal individuals have balance btwn pathogenic and regulatory T cells
 - T1D prone express too much pathogenic/too little regulatory
 - T1D protected are reverse
 - XLAAD
 - FOXP3 stop codon
 - Genetic defect can lead to type 1 diabetes in presence of other autoimmune disorders for abnormalities in regulatory T cell maturation
 - Tregs may play role in suppressing possible autoimmune disorders
- Cytokines: CD4 T cells
 - IL-12 --> Th1 --> IFN- γ , IL-2 --> cell-mediated immunity, autoimmunity, pro-inflammation, allograft rejection
 - IL-10 + IFN- α --> Tr1 --> IL-10 + TGF-b --> suppression/regulation
 - IL-4 --> Th2 --> IL-4/5 --> humoral immunity/anti-inflammatory
 - IL- β , IFN- γ , TNF- α --> oxidative stress --> NO production --> β cell death
- Role of Autoantibodies
 - Markers of disease
 - GAD65, IA-2, Insulin, Islet cell
 - Assays
 - Immunoprecipitation for GAD-65, IA-2 antibodies
 - Radioimmunoassay for insulin antibodies
 - Immunoperoxidase staining for islet cell antibodies
 - More antibodies --> increases probability of developing type II
- Conclusions
 - Type I DM is a polygenic disease w/ HLA DR3, DR4 having the strongest effect
 - CD4 and 8 T cell responses to islet autoantigens are pathogenic
 - Defect of Reg T cells in suppressing pathogenic autoimmune responses is assoc w/ Type I DM
 - Proinflammatory cytokines IL- β , IFN- γ , TNF- α can cause β cell death
 - Gene defects in FOXP3 and AIRE cause multiple autoimmune diseases incl. T1DM
 - Presence of antibodies to insulin, GAD-65, IA-2 are high risk markers of T1D progression