Is Autoimmunity on the Increase in Type 1 Diabetes Mellitus (T1DM)?
Presentation of Multiple Autoimmune Disorders at Diagnosis of T1DM

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Introduction

- T1DM results from autoimmune destruction of pancreatic beta islet cells and up to a 1/3 of patients develop autoimmune polyglandular syndrome (PAS)
- Autoimmune hypothyroidism (AIHT) is the most common disorder associated with T1DM with a prevalence between 5-31.5%
- Autoimmune non glandular problems like coeliac disease (CD) occur in 1 – 8.3% in children with T1DM
- Approximately 50 T1DM susceptibility genes have been identified and these genes also carry a potential risk for various autoimmune diseases occurring simultaneously or within a narrow time interval and might explain associated endocrine autoimmune diseases in one third of all T1DM patients
- We present two patients presenting at diagnosis with PAS and CD

Case Reports

Case 1

- 9 year old girl presented in diabetic ketoacidosis with a 3 month history of polyuria and polydipsia
- Initial TSH 97.5 mU/L (NR: 0.3-5.0) and Free T4 1.3pmol/L (NR: 12-22) Thyroid peroxidase antibody (TPO Ab) was normal and repeat TSH 75.6 mU/L and FT4 of 3.8 pmol/L, confirmed the diagnosis of AIHT
- Tissue Transglutaminase (tTG) >128 U/ml (NR: <10). She was heterozygous for HLA DQA1*05:01/DQB1*02:01 and negative for HLA-DQ8 (HLA-DQB1*03:02) consistent with a diagnosis of CD

Case 2

- 10 year old girl presented with two week history of polyuria, polydipsia and high blood glucose
- Initial TSH 9.2 mU/L and repeat test showed TSH 63.3 mU/L which confirms the diagnosis of AIHT
- Positive family history for CD
- tTG level was 170 U/ml and jejunal biopsy showed features of villous atrophy confirming CD

Discussion

T1DM & Hypothyroidism

- HLA DQ Polymorphism (HLA DQA1, DQB1, DQ2 and DQ8) can significantly modify the risk for CD and AIHT
- HLA DQB1*0302 is known to increase the risk of developing anti-thyroid antibodies and CTLA-4 gene polymorphism may play significant role in synergy with Human Leucocyte Antigen (HLA) for the development of AITD and T1DM
- Studies reported that 50% of children with elevated TPO Ab hypothyroidism in 3-4 years
- Majority of children with T1DM do not have symptoms of hypothyroidism
- Recurrent hypoglycaemias can be a presenting feature of hypothyroidism in TIDM due to decreased hepatic glucose production

T1DM & Coeliac Disease

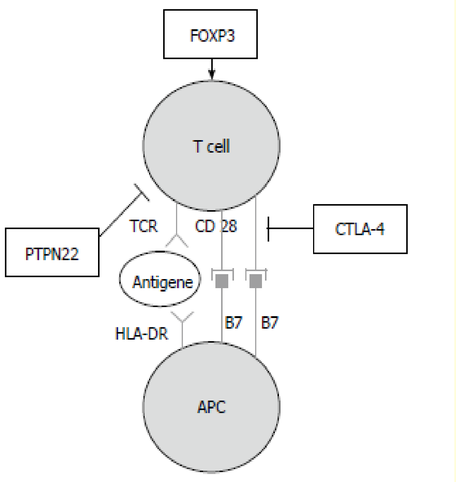
- HLA DQ2 and DQ8 genes increase the risk for developing TIDM and CD
- HLA DQ2 is prevalent in 20-30 % of population, and only a minority develop CD suggesting an additional non HLA linked genetic involvement
- TNF α is a major factor responsible for damaging small intestinal epithelium and increases the tTG levels
- TNF α has synergistic action with IL-6 to increase the HLA DQ gene expression which allows more gliadin into small intestinal epithelium and modulate the inflammatory response which leads to development of CD
- More than half of the children with T1DM who develop coeliac disease may be asymptomatic.IgA anti-tTG antibodies has high sensitivity (95.2%) and high specificity (95%) to detect CD in T1DM

Prevalence of Organ Specified Autoantibodies and Autoimmune Diseases

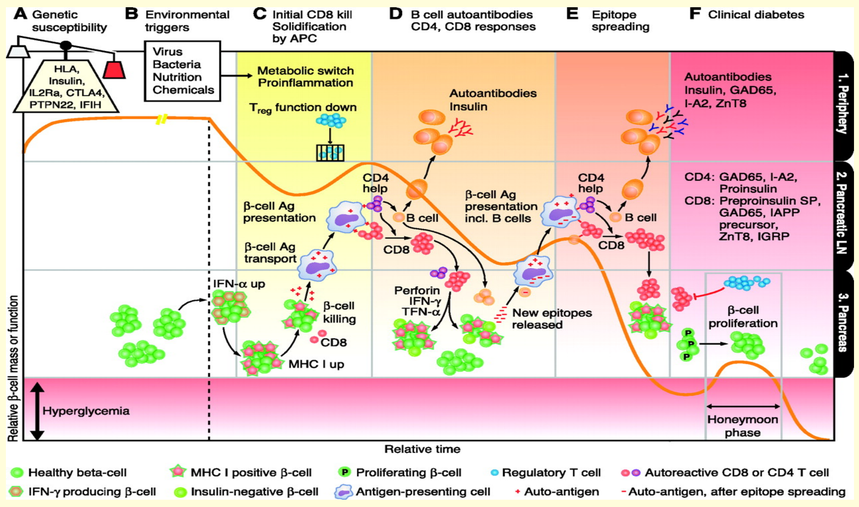
Disease or AB	General population	Type 1 diabetes mellitus	Coeliac disease	Addison's	Hypothyroidism
Type 1 diabetes mellitus anti-islet AB	2-3% 1-3%	xxx 85-90%		12-14%	4%
Coeliac transglutaminase AB	0.5% 0.5-1%	1-8% 8-12%	xxx 99%	5%	4%
Addison's 21-hydroxylase AB	0.005% 0-0.6%	0.5% 0.7-3%		xxx 83-90%	
Hypothyroidism	5-9%	30%	3-12%	14-21%	xxx
aTPO	2-10% in adults 1-4% in children	15-30% in adults 5-22% in children	18%	23-40%	47-83%
Graves' TSH receptor AB	0.1-2% ?	6-10% ?		10-20%	
Pernicious anaemia/ autoimmune gastritis PCA	2% for AIG 0.15-1% for PCA 2.5 - 12%	5-10% for AIG 2-4% for PCA 15-25% in adults 10-15% in children		6%	2%

AB = antibody; AIG = autoimmune gastritis; PCA = parietal cell antibodies; T1DM = type 1 diabetes mellitus.

Immunological Synapse in PAS



Interplay of Genetic, Environmental and Autoimmune Triggers



Conclusion

- T1DM patients exhibit increased risk of other autoimmune disorders, especially AIHT and CD in children
- Early detection of antibodies(Anti-tTG Ab and Anti-TPO Ab) and latent organ specific dysfunction at the diagnosis or later in evolution of TIDM, is strongly advocated
- Metabolic control can be affected by concomitant autoimmune conditions in children with T1DM, hence early detection and management reduces the morbidity
- Presentation of both autoimmune polyglandular and non glandular disease at diagnosis is rare, suggesting a complex interplay of genetic (HLA and non HLA linked genes, environmental and immunological factors

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