Immunologic Features
22q11.2DS

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Objectives

- Genetics and DiGeorge Syndrome
- Thymus
- Immune cells (T-, B-, and NK cells)
- 22q11.2DS-associated disorders
  - autoimmune and allergic diseases
- Treatment
- Vaccines
- References
Genetics of 22q11.2 deletion syndromes

- DiGeorge syndrome (DGS)
  - >90% associated with chromosome 22q11.2 deletion
  - lesser associated with 10p14 deletion, chromodomain helicase DNA binding protein (CHD7), prenatal exposure to isotretinoin, high glucose

- Velocardiofacial syndrome
  - 80-100% have 22q11.2 deletion

- Immune deficiency is a part of DGS and not correlated with degree of other phenotypic features
DiGeorge Syndrome

- Cardiac anomalies
- Immunodeficiency
- Hypocalcemia from parathyroid gland hypoplasia

Nomenclature
- The term 22q11.2 deletion syndrome is used to refer to patients who have the deletion and DiGeorge Syndrome (DGS) is used when relying on clinical features
Thymus

- Thymic hypoplasia – partial DGS
  - decreased T cells
  - 75-80% of infants

- Thymic aplasia – complete DGS
  - absence of T cells
  - corresponding humoral defects – low antibodies
  - 1% of infants

- Normal T-cell counts in 20% of patients

- Thymus size not predictive of T-cell counts
T-cells

- T-cell numbers range from none (complete DGS) to normal (partial DGS)
- Improves first year of life
  - homeostatic expansion vs generation of new cells
  - rate of decline is slower than controls
- Reduced T-cell receptor repertoire
- 22q11.2DS patients with a defect in IL-7Ra
  - IL-7 signaling is crucial for survival, expansion, and homeostasis of naïve CD4+ T-cells
B-cells and NK cells

- B-cells usually intact
- 22q11.2 deletion associated with increase of:
  - IgA deficiency
  - Specific Antibody Deficiency
- Recent studies suggest functional NK (natural killer) cell defects in pDGS
  - Cutaneous viral (e.g. warts and molluscum)
Infections

- Most common:
  - recurrent otitis media (ear infections)
    - monitor for hearing loss
    - Palatal dysfunction – ability to close of nasopharynx
  - recurrent sinusitis
- Also with recurrent bronchitis and pneumonia
- Fungal, Pnuemocystis, and viral infections in complete DiGeorge Syndrome (DGS)
Autoimmune Disorders

- Affects 10-23% of patients with 22q11DS
- Mechanism:
  - Reduction of Treg (CD4^+CD25^+ cells)
  - Compensatory expansion of T-cells
- Children
  - Juvenile rheumatoid arthritis
  - Immune thrombocytopenia
  - Autoimmune hemolytic anemia
  - Inflammatory Bowel Disease (e.g. Celiac disease)
- Adults
  - Psoriasis
  - Vitiligo
  - Rheumatoid arthritis
  - Immune thrombocytopenia
Atopic Disease

- Increased prevalence of atopy (Th2 skewing) in partial DGS
- Environmental allergies ("hayfever")
- Atopic dermatitis (eczema)
- Asthma
Treatment

- Humoral (B-cell) defects – antibodies
  - immunoglobulin replacement therapy
- Cellular (T-cell) defects
  - thymus transplantation
  - peripheral T-cell transplantation (fully matched)
  - antibiotic prophylaxis
    - antifungal, antiviral, antipneumocystis
- Blood products: CMV-negative and irradiated
- Thymus-sparing cardiac surgery
Vaccines

- No live vaccines without T-cell phenotyping
  - yellow fever, varicella-zoster, MMR, rotavirus, nasal influenza (injectable influenza is fine)
- Only give live vaccinations if:
  - CD4$^+$ cells >400 cells/mm$^3$ (= CD8$^+$ >200 cells/mm$^3$)
  - Adequate mitogen proliferation of T-cells
- Delay or holding vaccines have resulted in infections
  - 63% of unvaccinated children were infected with varicella (chicken pox)
References I


References II


