Chronic Granulomatous Disease: An Overview

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First described in 1954:

Hypergammaglobulinemia Associated with Severe Recurrent and Chronic Nonspecific Infection. Dr. Charles A. Janeway, Boston, Dr. John Craig (by invitation), Boston, Dr. Murray Davidson (by invitation), New York, Dr. William Downey (by invitation), New Bedford, Mass., Dr. David Gitlin (by invitation), Boston, and Julia C. Sullivan, M.P.H. (by invitation), Boston.


And defined in 1959:

A Fatal Granulomatous Disease of Childhood

The Clinical, Pathological, and Laboratory Features of a New Syndrome

Robert A. Bridges, M.D.; Heinz Berendes, M.D., and Robert A. Good, M.D., Ph.D., Minneapolis

AMA Journal of Diseases of Children, 1959
So What is CGD?

- A disorder of phagocytes (a type of white blood cell)
- Phagocytes cannot kill some bacteria and fungi because they cannot make an oxidative burst resulting in:
  - Severe infections from “bugs” that would not necessarily cause a bad infection in someone without CGD
  - Inflammation
- It is important to know that the other parts of the immune system (antibody production, complement activation, etc.) are NORMAL
White Blood Cells

Types:

Phagocytes are neutrophils and monocytes
Phagocytosis

1. Chemotaxis
2. Attachment
3. Phagocytosis
4. Destruction
Characteristics

- Inherited disease
  - X-linked inheritance
  - Autosomal recessive inheritance
- ~1:200,000 births (in the US: ~20 babies annually)
- Boys affected more than girls (~ 2:1)
- Usually presents in early years of life (aged 1-3)
- Presentation is usually acute or recurrent bacterial infections
- Sometimes presents as early onset inflammatory bowel disease
CGD may present at any time from infancy to adulthood\(^1,2\)

- Median age at diagnosis is 2.5 to 3 years\(^1\)
- Age at diagnosis is older for people with autosomal recessive vs X-linked mode of inheritance\(^3-5\)


(Slide used with permission of HorizonPharma)
X-linked inheritance

xy-Male  xx-female  x-x chromosome carrying CGD
### Autosomal Recessive Inheritance

<table>
<thead>
<tr>
<th>D-normal gene</th>
<th>d-CGD gene</th>
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<tbody>
<tr>
<td><strong>Both parents carriers of CGD</strong></td>
<td><strong>One parent a carrier of CGD</strong></td>
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D: normal gene, d: CGD gene
## Autosomal Recessive Inheritance

<table>
<thead>
<tr>
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<th>Both parents are carriers of CGD</th>
<th>Both parents have CGD</th>
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- **D** represents the normal gene.
- **d** represents the CGD gene.
Assess the **oxidative burst** which is what kills the bacteria or fungi after the phagocytes attach to the germ and surround it

Tests:

- **Nitroblue tetrazolium test (NBT):**
  - Qualitative test - person has CGD or does not
- **Dihydrorhodamine neutrophil burst assay (DHR); the “Gold Standard”**
  - Quantitative test that can distinguish between x-linked disease, autosomal recessive disease, and carrier status

Limitations
Diagnosis: Nitroblue Tetrazolium Test

negative

positive (normal)
Presentation: Infections

- Especially in:
  - Lymph nodes
  - Lungs
  - Liver
  - Skin

- Caused by “CGD” pathogens (usually bacteria or fungi that produce an enzyme called catalase)

- Don’t get better or take a long time to treat with appropriate treatment

- Recur
Typical CGD Pathogens

- *Staph aureus* (50-60% of infections)
- *Burkholderia cepacia*
- *Serratia marcesens*
- *Nocardia*
- *Candida*
- *Aspergillus*
Presentation: Granuloma Formation

- **Gastrointestinal system**
  - Granulomata found throughout the GI tract
  - Can cause abdominal pain, diarrhea, strictures and fistulae
  - Can mimic Crohn’s disease

- **Genitourinary System**
  - In the bladder, urethra and ureters
  - Can cause pain and obstruction
Co-morbidities (other illnesses)

- **Autoimmune disease**
  - Eyes: inflammation of the cornea, retina and uvea
  - Kidneys: IgA nephropathy
  - Joints: Juvenile arthritis
  - Myasthenia gravis
  - Skin: Raynuad’s phenomena, light sensitivity, rash