

Chronic Granulomatous Disease - CGD

Clinical Background

Chronic granulomatous disease (CGD) is an uncommon inherited disorder of the nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase complex and is characterized by recurrent, severe infections.

Epidemiology

- Incidence – 1/200,000 births
- Age – mean diagnosis from birth to as late as 65 years
- Sex – M>F by 85%

Inheritance

- Both X-linked (65-70%) and autosomal recessive forms
- X-linked form involves mutations in the 13 exons encoding the 91 Kd heavy chain of cytochrome b558 in the *CYBB* gene
- Most common autosomal recessive form involves mutations in the 47 Kd cytosolic phagocyte oxidase (20-25%) on chromosome 7; two other AR forms make up 5-10% of cases and involve the 67 Kd cytosolic factor encoded on chromosome 1 and the 22 Kd light chain of the cytochrome b558 in the *CYBA* gene

Pathophysiology

- Function of neutrophils
 - Neutrophils are the first line of defense against bacterial and fungal infections
 - Neutrophils migrate to the site of infection where phagocytosis then occurs
 - Neutrophil granules fuse to the phagosome, and, in addition, microbicidal reactive oxygen products are generated
- CGD is a result of problems with neutrophils that cause defective microbicidal oxidant production secondary to a defect in the neutrophil respiratory burst
 - Defects result in decreased production of superoxide, hydrogen peroxide, hydroxyl radical and hypochlorite ion within neutrophil and macrophages
 - Most common infections are bacterial infections produced by catalase-positive microorganisms and fungal organisms
 - Disorder makes patients susceptible to infectious organisms that may be nonpathogenic in the normal host
- Molecular defects associated with disease result in a malfunction of one of the phagocyte NADPH oxidase components

Clinical Presentation

- Clinical manifestations usually appear very early in childhood, but may not present until later in life, especially with autosomal recessive or variant forms of X-linked CGD
- Gastrointestinal – nausea, diarrhea, vomiting, colitis with inflammatory bowel disease (IBD)-like manifestations
- Genitourinary – urethral strictures, bladder granulomas
- Pulmonary – pneumonia
- Skin and musculoskeletal – lymphadenitis, skin and visceral abscesses, osteomyelitis
- Infections
 - Eventual chronic obstructive granulomas form at sites of infection

- Characterized by bacterial and fungal infections
- Increased tendency toward development of certain autoimmune diseases
 - Sarcoidosis
 - IBD-like manifestations with colitis, blood in stool and granuloma in GI tract

Treatment

- Early diagnosis and aggressive therapy, including use of interferon gamma and fungal and bacterial prophylaxis, markedly improves prognosis
- Recent studies indicate successful results in transplanted patients and gene therapy as a future possibility
 - Bone marrow and stem cell transplant may be curative

Diagnosis

- Indications for testing – severe and recurrent bacterial and fungal infections, presence of granulomas, colitis, pneumonias
- Laboratory testing
 - Neutrophil oxidative burst assay (DHR) via flow cytometry – disease indicated by absence of activity
 - Other less-reliable tests include measurement of superoxide production, ferrocyanide reduction, nitroblue tetrazolium test (NBT)
- Non-specific testing – to rule out other disorders
 - Serum quantitative immunoglobulins
 - Complement activity enzyme immunoassay
 - CBC with differential
 - Myeloperoxidase stain
 - Neutrophil receptor profile
- Genetic testing
 - Molecular methods (PCR) to identify mutations via high-resolution melting analysis on a research basis at present.

Differential Diagnosis

- Other primary immunodeficiency syndromes
 - Hypogammaglobulinemia
 - Complement deficiency
 - Leukocyte adhesion deficiency type 1
 - Hyper IgE syndrome (Job syndrome)
 - Kostmann agranulocytosis
 - Autoimmune neutropenia
 - Myeloperoxidase deficiency
 - Innate immune deficiency
- Inflammatory bowel disease
- Sarcoidosis

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Neutrophil Oxidative Burst Assay (DHR) 0096657 Method: Flow Cytometry	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD) Characterize autosomal recessive CGD and X-linked carrier status	Test results alone not diagnostic Test is time sensitive	For abnormal results, ARUP encourages consultation with medical director of Immunology Laboratory
Immunoglobulins, Serum Quantitative 0050630 Method: Nephelometry	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD) Panel includes IgA, IgG, IgM		
Complement Activity Enzyme Immunoassay, Total 0050198 Method: Enzyme-Linked Immunosorbent Assay	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD)		
CBC with Platelet Count & Automated Differential 0040003 Method: Automated Cell Count with Flow Cell Differential	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD)		
Myeloperoxidase Stain 0049030 Method: Cytochemical Stain	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD)		
Neutrophil Receptor Profile 0095921 Method: Flow Cytometry	Use along with other clinical findings to diagnose chronic granulomatous disease (CGD) Panel measures CD11b, CD15, CD16, and CD18 on neutrophils	Time sensitive	

Guidelines

Practice parameter for the diagnosis and management of primary immunodeficiency. American Academy of Allergy, Asthma and Immunology - Medical Specialty Society. American College of Allergy, Asthma and Immunology - Medical Specialty Society. Joint Council of Allergy, Asthma and Immunology - Medical Specialty Society. 1995 August 31 (Revised 2005 May).

General References

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Immunodeficiency Evaluation for Chronic Infections in Adults and Older Children Testing Algorithm

Immunodeficiency Evaluation for Chronic Infections in Infants and Children Testing Algorithm

Related Content

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Neutrophil Disorders

Severe Combined Immunodeficiencies - SCID

T-Cell Deficiency Disorders, Inherited

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