WHIM Syndrome Treatment: We Can Do Better

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Resource Information

About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled WHIM Syndrome (A Chronic Neutropenic Disorder): Uncouple the Complex for HCPs and Patients

Program Learning Objectives:

- Gain an understanding of WHIM syndrome as a rare PID/ chronic neutropenic disorder with diverse clinical presentations
- Implement strategic measures to improve the early identification of WHIM syndrome patients for prompt assessment and diagnosis to avoid potential complications and long-term sequelae
- Understand the CXCR4 pathway dysregulation and how it relates to the underlying causes of WHIM syndrome
- Garner an understanding of the limitations of current approaches for WHIM syndrome and potential new approaches for patients

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WHIM Syndrome Case Study:

A challenging family with recurrent infections, hypogammaglobulinemia, neutropenia and lymphopenia

Index Patient (I-1), a 6-Year-Old Male

Index Case Medical History

- Pneumococcal pneumonia and sepsis
- Recurrent OM
- Amoxicillin prophylaxis

I-1
(6y)

Warts: No
Hypogamma +/-
Infections
Neutropenia

	Index patient	NR
ANC, $x10^9$/l	0.2-0.4	1.8-7.4
Lymphocytes, $x10^9$/l	0.8-1.4	0.8-3
IgG, g/l	4.3-6-9	5.0- 14.6
CD4, cells/ul	540	>450
CD8, cells/ul	160	>220
CD19, cells/ul	30	>100

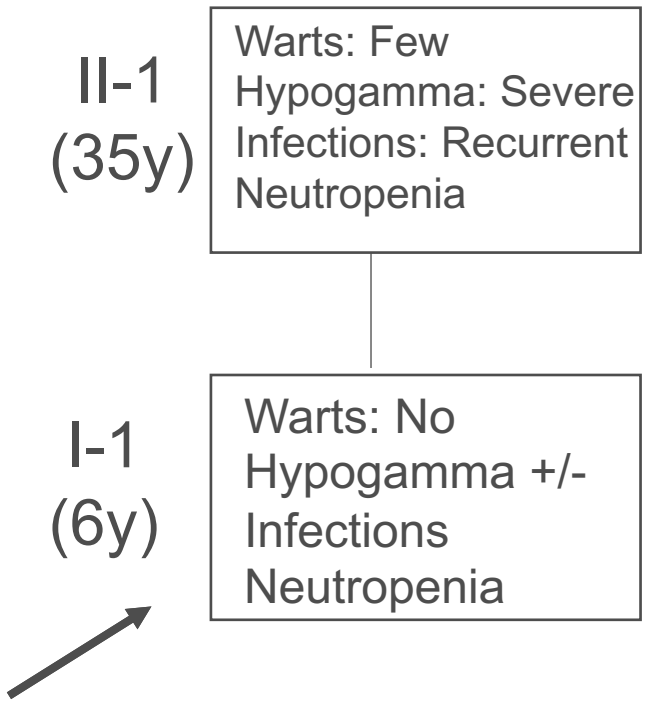
Normal IgM, IgA, and normal antibody responses to tetanus, MMR, pneumovax, isohemagglutinins

Hypogamma, hypogammaglobulinemia; MMR, measles mumps and rubella; NR, normal range; OM, otitis media.
Grunebaum E & Roifman CM. *Pediatric Academic Societies.* 2007.

35-Year-Old Father (II-1)

Medical History

- Upper and lower respiratory track infections in childhood
- Few warts on fingers
- Sinusitis, pericarditis, lymphangitis epididymitis/prostatitis x 2
- Known low blood count, not investigated



	Father	NR
ANC, $x10^9$/l	0.4-0.6	1.8-7.4
Lymphocytes, $x10^9$/l	0.3-0.5	0.8-3
IgG, g/l	2.4	7.2-15.8
CD4, cells/ul	182	>450
CD8, cells/ul	29	>220
CD19, cells/ul	5	>100

- Low IgM (0.2) and IgA (0.4)
- Normal antibody responses to polio and MMR
- Poor response to tetanus, pneumovax and isohemagglutinins

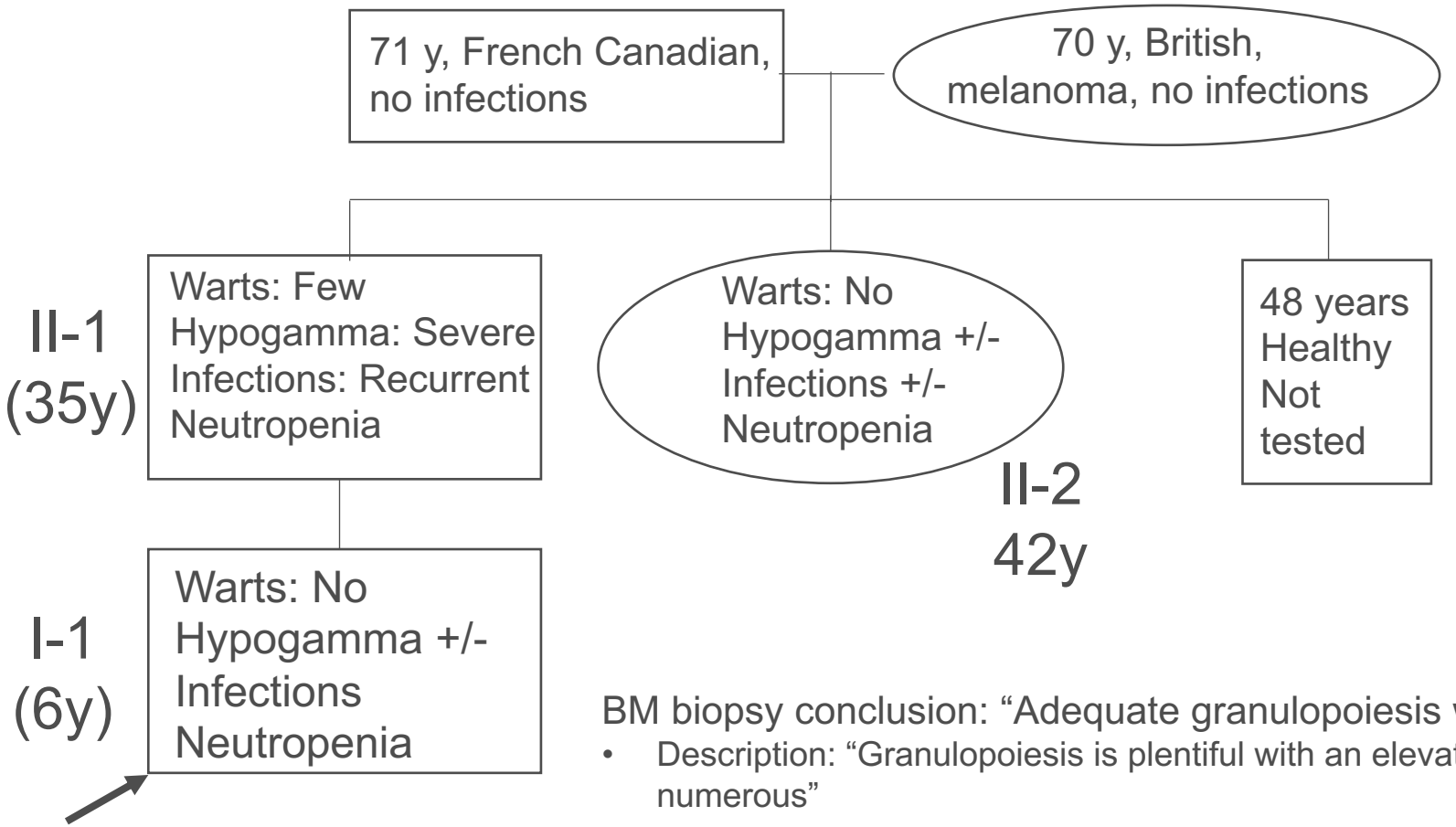
Due to recurrent infections, low IgG and poor antibody responses, Dad started Ig replacement.

Hypogamma, hypogammaglobulinemia; Ig, immunoglobulin; MMR, measles mumps and rubella; NR, normal range.

42-Year-Old Female Aunt (II-2)

Medical History

- Recurrent sinusitis and OM from 36 years
- Few in childhood
- Urinary tract infections
- Past neutropenia, not investigated
- No warts



	Aunt	NR
ANC, $x10^9$/l	0.2	1.8-7.4
Lymphocytes, $x10^9$/l	0.4	0.8-3
IgG, g/l	5.2	7.2-15.8
CD4, cells/ul	200	>450
CD8, cells/ul	80	>220
CD19, cells/ul	20	>100

- Normal IgA and IgM
- Normal antibody responses to tetanus, MMR-V, pneumovax
- Poor response to isohemagglutinins

BM biopsy conclusion: “Adequate granulopoiesis with normal maturation”

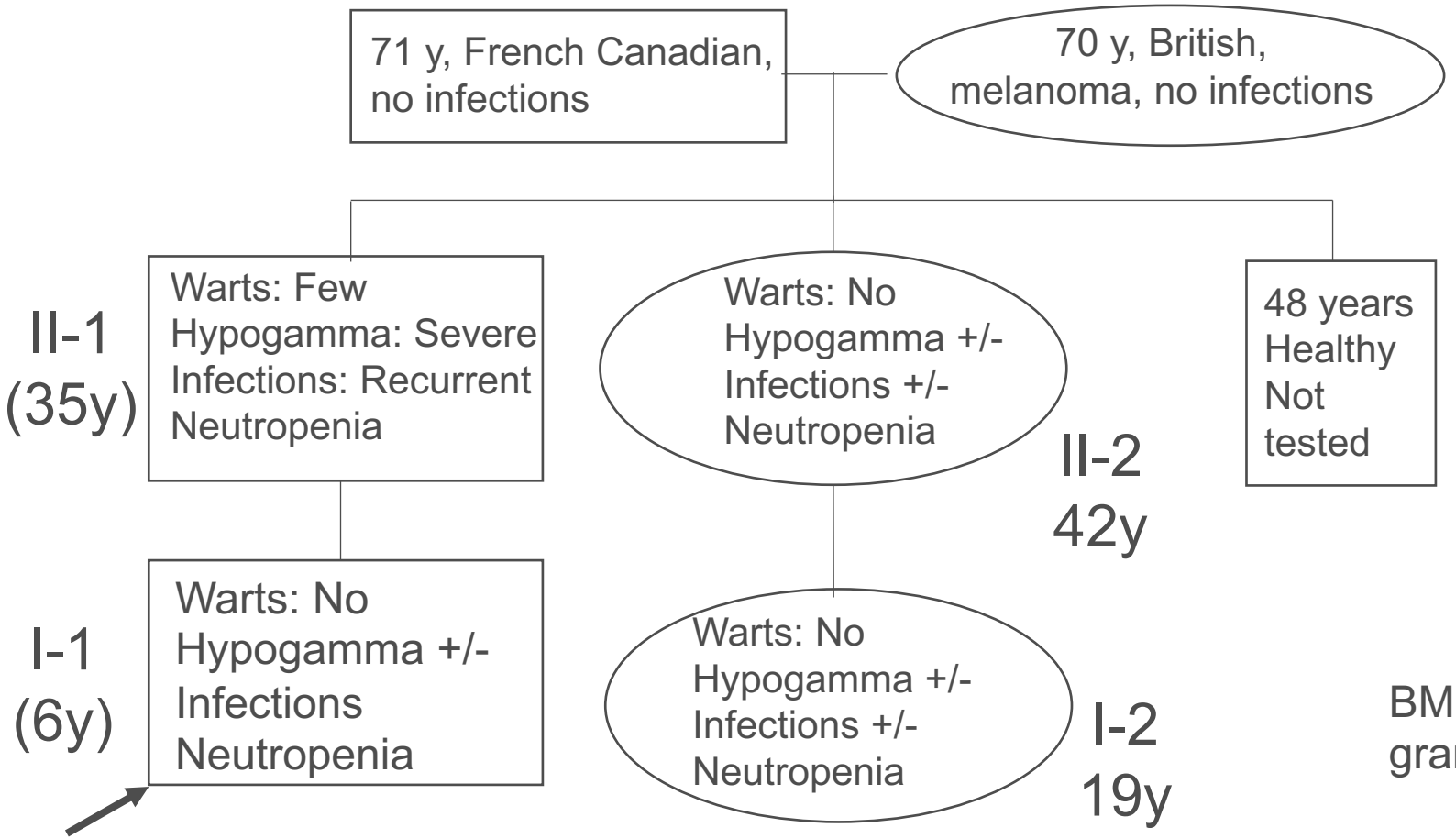
- Description: “Granulopoiesis is plentiful with an elevated M/E ratio. Segmented neutrophils are numerous”

BM, bone marrow; hypogamma, hypogammaglobulinemia; M/E, myeloid/erythroid; MMR, measles mumps and rubella; NR, normal range; OM, otitis media.

19-Year-Old Female Niece (I-2)

Medical History

- Neutropenia from birth
- OM at 6 years
- Strep throat at 14 years
- Recurrent sinusitis



	Niece	NR
ANC, x10^9/l	0.3	1.8-7.4
Lymphocytes, x10^9/l	0.8	0.8-3
IgG, g/l	5.5- 7.0	7.2-15.8
CD4, cells/ul	480	>450
CD8, cells/ul	150	>220
CD19, cells/ul	40	>100

- Normal IgA, IgM
- Normal antibody responses to tetanus, MMR-V, pneumovax and isohemagglutinins

BM biopsy conclusion: “Adequate mature granulocytes and granulocyte precursors.“

BM, bone marrow; hypogamma, hypogammaglobulinemia; MMR, measles mumps and rubella; NR, normal range; OM, otitis media.

Phenotypic Diversity in a Family with Recurrent Infections, Hypogammaglobulinemia, Neutropenia and Lymphopenia

	Sex	Age	Warts	Infections	Hypogamma	Myelokathexis/ neutropenia	B cells Cell/ul
Index (I-1)	Male	6y	No	Yes	Borderline: Yes	ND/yes	40
Father (II-1)	Male	35y	Few	Yes	Yes: Profound	ND/yes	5
Aunt (II-2)	Female	42y	No	Mild	Borderline: Yes	??/yes	20
Niece (I-2)	Female	19y	No	Mild	Borderline	??/yes	80

Myelokathexis?? Not “called” initially, yet likely was present

Hypogamma, hypogammaglobulinemia; ND, not done.

Current Management

	Tx	Age started	Indications
Index (I-1)	SCIg	11y	Recurrent invasive infections, pneumonia, hypogamma
Father (II-1)	SCIg	35y	Recurrent invasive infections, profound hypogamma
Aunt (II-2)	SCIg	45y	Recurrent sinus/otitis (?), urinary tract infections (?), hypogamma, family Hx
Niece (I-2)	SCIg	27y	Recurrent sinus infection (?), hypogamma, family Hx

Hypogamma, hypogammaglobulinemia; SCIg, subcutaneous immunoglobulin replacement.

Multisystemic Clinical Manifestations in WHIM Syndrome

Leukopenia, neutropenia, and overall defective immune responses

WBC 2000 or less cells/μL
ANC less than 500 cells/μL
ALC less than 650 cells/μL

Impaired vaccine response (low vaccine titers)

Infection and infectious complications

EBV-associated lymphoproliferative disease

Recurrent sinopulmonary infections
- Otitis media
- Sinusitis
- Pharyngitis
- Pneumonia
- Upper respiratory tract infections

Cellulitis

Treatment-resistant HPV warts on hands, feet, and anogenital area

Periodontal infections
- Periodontitis
- Gingivitis

Long-term and life-threatening consequences

Sepsis

Lymphoma

Squamous cell carcinoma

Bronchiectasis, COPD

Cervical dysplasia and cancer

Skin abscesses

Hearing loss

Impaired quality of life

ALC, absolute lymphocyte count; AMC, absolute monocyte count; COPD, chronic obstructive pulmonary disease; EBV, Epstein–Barr virus; HPV, human papillomavirus; WBC, white blood cell count.

Heusinkveld LE, et al. *Expert Opin Orphan Drugs*. 2017;5(10):813-825; Al Ustwani O, et al. *Br J Haematol*. 2014;164(1):15-23; McDermott DH, et al. *Immunol Rev*. 2019;287(1):91-102; Heusinkveld LE, et al. *J Clin Immunol*. 2019;39(6):532-556; Data on file. X4 Pharmaceuticals Inc.; Dotta L, et al. *Curr Mol Med*. 2011;11(4):317-325; Gorlin RJ, et al. *Am J Med Genet*. 2000;91(5):368-376; Badolato R, et al. *Blood*. 2017;130(23):2491-2498; Dale DC, et al. *Blood*. 2020;136(26):2994-3003; Beaussant Cohen S, et al. *Orphanet J Rare Dis*. 2012;7:71.

Current Management of WHIM Syndrome

- Patients with WHIM syndrome experience significant disease burden that affects their quality of life
- Current approved treatment is
  - Symptomatic only, not targeted
  - Not systematically evaluated in WHIM syndrome
  - Not effective in prevention or treatment of HPV-associated warts

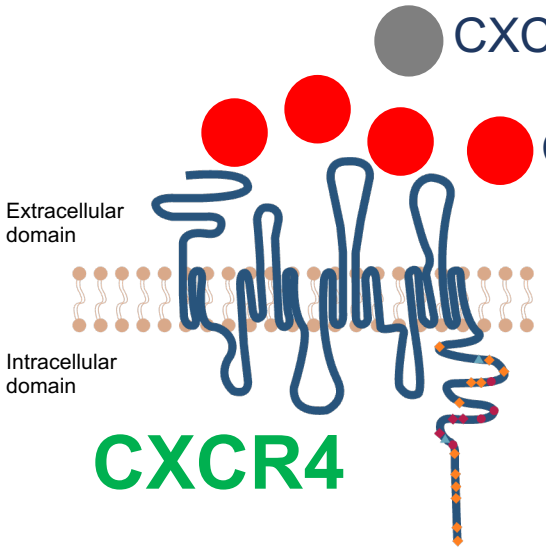
Symptomatic Management of WHIM Syndrome

Category of Therapeutics	Role in the Management of WHIM Syndrome
Antibiotics	• May attenuate the risk of exacerbations • Low-dose macrolides and inhaled aminoglycosides may reduce risk of bronchiectasis exacerbations
Antivirals	• Effective against recurrent herpes infections
IGs	• May reduce incidence of recurrent infections • No well-controlled studies documenting efficacy in WHIM syndrome • Not approved by FDA specifically for WHIM syndrome
CSFs	• Used to increase levels of circulating neutrophils • No well-controlled studies documenting efficacy in WHIM syndrome • Not approved by FDA specifically for WHIM syndrome

FDA, Food and Drug Administration.

Badolato R, et al. *Blood*. 2017;130(23):2491-2498; Heusinkveld LE, et al. *Expert Opin Orphan Drugs*. 2017;5(10):813-825; Heusinkveld LE, et al. *J Clin Immunol*. 2019;39(6):532-556; McDermott DH, et al. *Immunol Rev*. 2019;287(1):91-102; Bonilla FA, et al. *J Allergy Clin Immunol*. 2015;136(5):1186-1205.

Novel Treatment Approach in Research Phase – CXCR4 Antagonists



Mechanism of Action:

- Binds to CXCR4 and blocks the binding of its cognate ligand CXCL12
- Downregulate signaling and allow for internalization of receptor
- Improved mobilization of stem cells and neutrophils from bone marrow

1. **Plerixafor (Mozobil)** (intravenous administration):
   - FDA approved for mobilization of hematopoietic stem cells from bone marrow to blood in combination with granulocyte-colony stimulating factor (G-CSF) for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM).
2. **Mavorixafor (Mozobil)** (oral administration):
   - No FDA approval, currently in clinical trials

G-CSF, granulocyte-colony stimulating factor, MM, multiple myeloma; NHL, non-Hodgkin’s lymphoma.

Summary

- WHIM is a rare, autosomal dominant primary immunodeficiency disorder with no approved therapy
- Patients with WHIM have pathogenic variants in the CXCR4 gene, which results in retention of neutrophils, lymphocytes, and monocytes (myelokathexis) in the bone marrow, leading to leukopenia and inadequate immune function
- WHIM stands for warts, hypogammaglobulinemia, infections, and myelokathexis; however, the acronym does not reflect the broad spectrum of disease manifestations that patients may experience
- Clinical manifestations of WHIM are associated with significant morbidity and mortality, and patients with WHIM often face delays in diagnosis and/or misdiagnosis
- Management strategies for WHIM are symptomatic only and address the substantial burden of disease

Heusinkveld LE, et al. *Expert Opin Orphan Drugs*. 2017;5(10):813-825; Badolato R, et al. *Blood*. 2017;130(23):2491-2498; McDermott DH, et al. *Immunol Rev.* 2019;287(1):91-102; Dotta L, et al. *Curr Mol Med*. 2011;11(4):317-325; Wetzler M, et al. *Am J Med*. 1990;89(5):663-672; Aghamohammadi A, et al. *J Clin Immunol*. 2017;37(3):282-286.

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