Review of Case Report Literature Highlights that WHIM Syndrome has Serious Long-term Outcomes Beyond Warts and Infections

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Introduction

WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) syndrome:

- Rare, autosomal dominant, immunodeficiency disease caused by a mutation in the *CXCR4* gene leading to abnormal immune cell trafficking.[1,2]
- *CXCR4* mutations cause receptor hyperactivation and leukocyte retention in patient bone marrow (myelokathexis), resulting in severe chronic neutropenia and lymphopenia.[1,2]
- The nomenclature for WHIM is derived from the classic phenotype, but this acronym does not reflect the broad spectrum of disease manifestations that patients may experience.[3,4]
- The clinical phenotype of WHIM is heterogeneous, and presentation can occur in children and adults.[3,4]
- Mutations in the *CXCR4* gene were identified as the cause of WHIM in 2003.[1]

Individuals living with WHIM syndrome:

- Experience severe, life-threatening, and frequent upper respiratory tract and systemic infections, often beginning in infancy.[5,6]
- Show a distinct and disproportionate increase in susceptibility to human papillomavirus (HPV) infections, manifesting as cutaneous and anogenital warts, which may progress to cervical and vulvar cancers.[6]
- Often face delays in diagnosis due to the absence of one or more of the four classic characteristics at presentation.[3]

To date, there have been no rigorous natural history studies of WHIM, and a thorough understanding of its full spectrum of clinical consequences is lacking.

Objective

- The primary objective of this literature review report was to reduce the gap in clinical knowledge by conducting a thorough medical literature review of published WHIM cases.

Methods

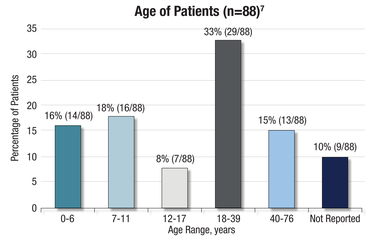
- A database of published information on patients with WHIM syndrome was constructed from case and cohort reports, comprising 88 cases with patient-specific data (case dataset)[7] and a cohort of 21 patients described by Dotta et al.[8]
- A total of 109 published WHIM cases were reviewed and consolidated in March 2018 **(Figure 1)**.
- A report including patient-specific data was constructed, providing a comprehensive overview of WHIM case study literature and lending insight into the prevalence of complications related to WHIM.

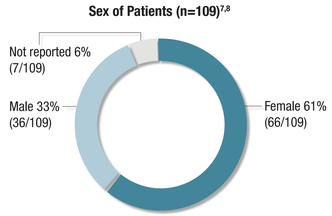
Figure 1. Sources reviewed for WHIM case report literature

Published Case Reports (n=88)[7] + **Cohort reported by Dotta (n=21)[8]** = **109 Published Cases Reviewed**

Results

Figure 2. Patient demographics[a]





[a]Age distribution was not reported for the cohort of 21 patients described by Dotta et al.

- *CXCR4* sequencing was reported in 77 patients.[7,8]
  - 51% (39/77) patients had R334X, the most common mutation identified in patients with WHIM.[1,7,8]
  - 35 other patients reported mutations, including 12 patients with S338X and 10 patients with frameshift mutations.[7,8]
  - 3 patients were reported as wild-type *CXCR4*.[7]
- Absolute lymphocyte count (ALC) <1×10^3 cells/µL (range 0.17-0.91x10^3 cells/µL) was observed in 19/34 (56%) patients in the case dataset, and was between 1×10^3 and 2×10^3 cells/µL for most but not all of the remainder.[7]
  - 67% (14/21) patients in the Dotta cohort reported lymphopenia, with an ALC of 0.8×10^3 cells/µL.[8]
- Patients with WHIM suffered from recurrent viral and bacterial infections.[7,8]
  - Multiple case studies documented infection with varicella zoster virus, oral herpes simplex virus, cytomegalovirus, Epstein-Barr virus-positive B-cell lymphoma, and rubella.
- Patients were susceptible to HPV infections that gave rise to warts, and none of the currently available treatments were adequate to prevent HPV infection or substantially reduce the burden of lesions.[7,8]
  - Notably, in a majority of patients, the warts-related phenotype of WHIM was incomplete, especially at onset.

Table 1. Summary of reported clinical characteristics of patients with WHIM

	Published Case Reports (n=88)[7]	Cohort Reported by Dotta (n=21)[8]	Combined Data (N=109)
Characteristic	**% (n/N)**	**% (n/N)**	**% (n/N)**
Pneumonia	39 (34/88)	57 (12/21)	**42 (46/109)**
Recurrent pneumonia	17 (15/88)	57 (12/21)	**25 (27/109)**
Leukopenia	67 (31/46)	100 (21/21)	**78 (52/67)**
Neutropenia	89 (48/54)	100 (21/21)	**92 (69/75)**
Warts	52 (46/88)	48 (10/21)	**51 (56/109)**
Anogenital warts	19 (17/88)[a]	14 (3/21)	**18 (20/109)**

[a]One additional patient had possible genital warts.

Results (cont'd)

Table 2. Severe complications and age at diagnosis in the case dataset of patients with WHIM[7]

Complication[a]	No. of Patients	Age at WHIM Diagnosis, years
Carcinoma of the vulva	3	39.5, 48, 73
Meningitis	5	16, 17, 17, 31, 36
Sepsis/septicemia	4	11, 24, 39.5, 52
Lymphoma	5	26, 31, 40, 40.6, 54
Bronchiectasis	10	10, 11, 23, 24, 27, 36, 39.5, 40.6, 44, 75.6
Hearing loss	3	4, 81, 82

[a]One patient experienced multiple severe complications, including pneumonia since childhood leading to chronic bronchiectasis; chronic sinusitis; genital herpes simplex virus 2; angiocholitis; chronic skin granuloma; sepsis; intestinal tract.

- Severe complications reported in both WHIM populations included hearing loss, lymphoma, meningitis, carcinoma of the vulva, and sepsis, summarized in **Table 2.**[7,8]
  - Patients were also found to have an increased risk of developmental defects. Tetralogy of Fallot was reported in 3 cases out of the first 90 identified patients with WHIM (prevalence in the general population of ~3/10,000 live births).[1,7,8]

Conclusions

- Challenges in clinical evaluation and the overall rarity of WHIM can contribute to delayed diagnosis or misdiagnosis as another primary immunodeficiency.
- The data described here can be used to:
  - Highlight the impact of WHIM on patient quality of life (QoL), as well as the seriousness of long-term complications in addition to warts and infections.
  - Address the diagnosis of WHIM, prevent misdiagnosis, and support the effective management of diagnostic challenges.
  - Promote early and effective management of WHIM, with a goal of decreasing vulnerability to both life-limiting infections and malignancies.
  - Aid in the development of novel treatments that address the primary underlying drivers of morbidity in WHIM.

References

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