Emerging Picture of Morbidity in Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) Syndrome

Blaine Cloud, PhD, Clinical SCORE, LLC, Marnie Hoolahan, MBA, The NemetzGroup LLC
X4 Pharmaceuticals, Inc., Cambridge, MA, USA

Research Summary

We reviewed existing published knowledge on WHIM as well as interviewed three patients about their experiences, to better understand how patients with WHIM syndrome present clinically and psychologically, showing a common medical history of some patients.

Introduction

WHIM syndrome is a rare, autosomal dominant primary immunodeficiency disease caused by a mutation in the *CXCR4* gene.[1] The condition was identified in 1964 and fully described in 1991 and named for its phenotypical features: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis. In 2003, the *CXCR4* mutation was identified paving the way for subsequent genetic testing availability.[2]

Patients with WHIM syndrome appear to have increased risk for human papilloma virus,[3] vulvar and cervical carcinoma,[4,5] lymphoproliferative disease/lymphoma,[6] as well as various life-threatening infections, including bronchiectasis and pneumonia.[7]

All four classic characteristics of warts, hypogammaglobulinemia, infections, and myelokathexis need not be present in a patient for a diagnosis of WHIM. Exacerbating WHIM's infrequency, this variability in presentation has led to underdiagnosis and underappreciation of the condition among patients and physicians alike.[8]

Management of many rare diseases is driven predominantly by patients. Due to low prevalence, healthcare providers typically have insufficient expertise in rare conditions to offer the highly specialized treatment needed. This forces the patient to become an expert in his/her disease.[9]

Research Hypothesis

Having a rare disease with cancer and infection risks, WHIM patients will display both strong self-advocacy and urgency in seeking an accurate diagnosis to preserve full length of life.

Methods

An extensive literature search was conducted using PubMed and Google Scholar. Search terms included: "chronic neutropenia, idiopathic neutropenia, lymphopenia, leukopenia, primary immune deficiency, primary immunodeficiencies, idiopathic gammaglobulinemia, idiopathic bronchiectasis, non-CF bronchiectasis, *CXCR4*, warts, hypogammaglobulinemia, infections, myelokathexis, WHIM, WHIM syndrome, and plerixafor."

A case study methodology was used. Patients were interviewed using a structured two-hour interview guide. Interviews covered childhood, adolescent, and adult health history as well as query into psychological reactions to medical conditions. Results were qualitatively analyzed.

Results: Patient Histories

Participants:

Three (3) female patients diagnosed with WHIM were genetically confirmed to carry the *CXCR4* mutation.

Patient 1
Diagnosed late in life, this 60+ yo WHIM patient has a long history of infections and cancers since childhood

Upper respiratory tract infections, with chronic cough throughout childhood and adulthood

- 1 – 10 years: Diagnosed with severe neutropenia.
- 11 – 20 years: Infection from insect bite becomes severe, painful abscess; misses work for 3 months and takes 1.5 years to heal. Four skin cancer lesions removed. Hospitalized for pneumonia several times.
- 21 – 40 years: Several prolonged skin infections. Warts first appear on hands.
- 41 – 60 years: Removal of boney polyps in ear. Abnormal pap smears over 15 years. Warts continue on hands.
- 61+ years: Fewer infections. Genetically confirmed for WHIM syndrome along with her son.

Patient 2
Diagnosed in childhood, this 30+ yo WHIM patient is relatively healthy despite long history of infections and recent cancer scares

Upper respiratory tract infections, with frequent bronchitis, pneumonia, and warts

- 1 – 4 years: Cat scratch leads to month-long hospitalization for infection. Diagnosed with neutropenia; then with WHIM.
- 5 – 10 years: Warts start on bottom of feet. Exercise-induced asthma.
- 11 – 20 years: Hospitalized for pneumonia almost every other year. Used nebulizer to control chronic bronchitis.
- 20 – 31+ years: Monitored for "suspicious moles". Body-piercings get infected. Hospitalized twice for pneumonia. Monthly sinus infections. Annual recurrent ovarian cysts, lead to oophorectomy. Recurrent urinary tract infections; one severe kidney infection.

Patient 3
Diagnosed as infant given family history of WHIM, she is in her 20s and has a history of recurrent infections

Upper respiratory tract infections; has "standing order" for antibiotics

- 1 – 4 years: Genetic diagnosis of WHIM. Severe cellulitis leads to first hospitalization. Hundreds of warts.
- 5 – 10 years: Frequent ear and sinus infections. Allergies develop and exacerbate sinus infections.
- 11 – 20 years: Multiple episodes of cellulitis. Several sinus infections per year.
- 21+ years: Hundreds of warts continue on hands and feet. Sinus infections less frequent now with aggressive use of prophylactic antibiotics.

WHIM patients were each in a different decade of life: 20s, 30s, and 60s. Given WHIM is a relatively newly identified condition, the oldest patient wasn't diagnosed until her 60s.

Patients had psychological commonalities:

- Patients miss important personal events due to sickness and hospitalizations
- Require repeated medical care from many different healthcare specialists
- Patients were ego-dystonic with their medical history and WHIM

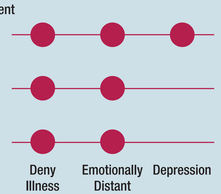
Only one patient tells her medical specialist that she's been diagnosed with WHIM, the other two patients self-identify as neutropenic patients. Paradoxically, their personalities appear to have been affected by lifelong sickness and fear of germs as patients keep emotional distance from others and some struggled with isolation and episodes of depression. WHIM patients do not fully incorporate their complex health conditions into their psychological outlook and thus do not consider themselves sickly.

Patients did not spontaneously admit to having warts, and their wart history needed to be drawn out through probing. Patients did not connect an association between their WHIM diagnosis, warts, or possible HPV-positive status to a cancer risk. In the case of WHIM, patients do not fully appreciate what WHIM means to them and their health and they do not seem to appreciate that respiratory conditions, warts, gynecologic problems, cancer risks, and their readily apparent infection history are tied by one genetic mutation and disorder that could shorten their lives.

Insights

- "I don't like to go out, especially in crowds."
- "If I knew someone else with WHIM syndrome, they may be able to give me advice and share their experiences to make me feel less alone."
- "I'd never tell any of my doctors that I have WHIM unless they need to know."

Analysis



Conclusions

WHIM syndrome's infrequency and heterogeneous phenotypes have prevented physicians from appreciating the full picture of its symptoms and prognosis. WHIM was only recently characterized as a named genetic syndrome; in fact only 109 patients have been identified in published literature to date. Many of the 109 cases provide insights into the morbidity and mortality of the syndrome but none provide the psychosocial and emotional insights gleaned through this small patient research.

This research suggests there are emotional and psychosocial manifestations of WHIM stemming from its broad spectrum of medical complications. Not only does this result fail to confirm the hypothesis of this study, results show patients do not advocate for medical management of WHIM and in fact may "hide" their diagnosis from healthcare providers.

- WHIM patients do not appreciate the impact of their disease on their own morbidity and mortality
- WHIM patients do not advocate for medical management of WHIM and may "hide" their diagnosis from healthcare providers
- The medical community requires education and awareness about the constellation of symptoms (many common and unsuspecting), illnesses, and psychological reaction associated with WHIM syndrome

The medical community requires education and awareness about the constellation of symptoms (many common and unsuspecting), illnesses, and psychological reaction associated with WHIM syndrome. This is critical because patients with WHIM syndrome – unlike other rare diseases – do not understand how their unique constellation of disparate medical symptoms puts them at serious health risks and they do not advocate for better care. Medical professionals should be aware of the genetic testing for this mutation.

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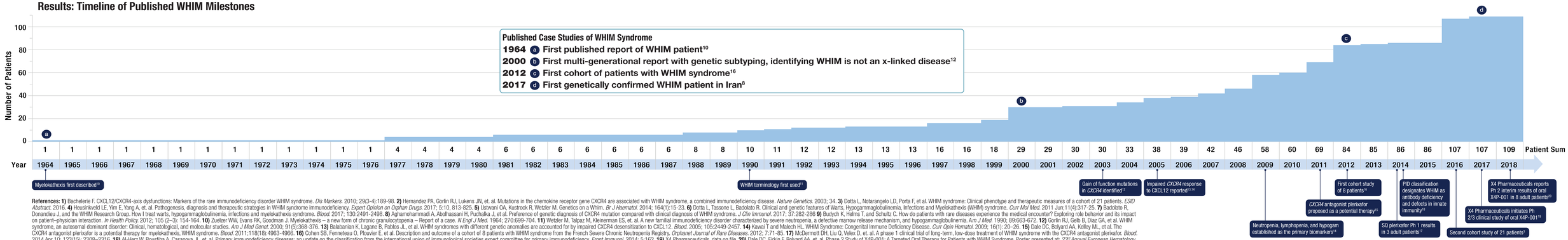
Results: Timeline of Published WHIM Milestones



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