MORE THAN JUST “**BRAIN FOG**” – NAVIGATING THE NEUROCOGNITIVE MANIFESTATIONS OF **VEXAS SYNDROME**

Dr. Gurmeet Sohi, MD FRCP Geriatric and Internal Mediicne

OBJECTIVES

1. Identify the clinical hallmarks of VEXAS syndrome
2. Review the cognitive and neurological sequelae of VEXAS syndrome and differentiate from other neurodegenerative disorders
3. Consider interdisciplinary approach to management

CASE

- 69 year old male, from home with sister, presenting with subacute history of weakness, confusion and functional decline NYD
- In previous years, had episodes of an inflammatory, steroid responsive syndrome
  - Episode 1: cognitive decline, organizing pneumonia, small joint synovitis
    - Discharged to LTC due to cognitive/functional decline, MMSE 12/30 done prior to discharge
  - Episode 2: encephalopathy, generalized weakness, diffuse arthralgias, worsening organizing pneumonia, PET avid lymphadenopathy, high ferritin, pancytopenia. Bone marrow biopsy showed hemophagocytosis and vacuolization
    - Improved with prednisone
- In the past year and half, he is functionally independent, traveling independently without cognitive concerns

“Medicine is a science of uncertainty and an art of probability.”

– SIR WILLIAM OSLER

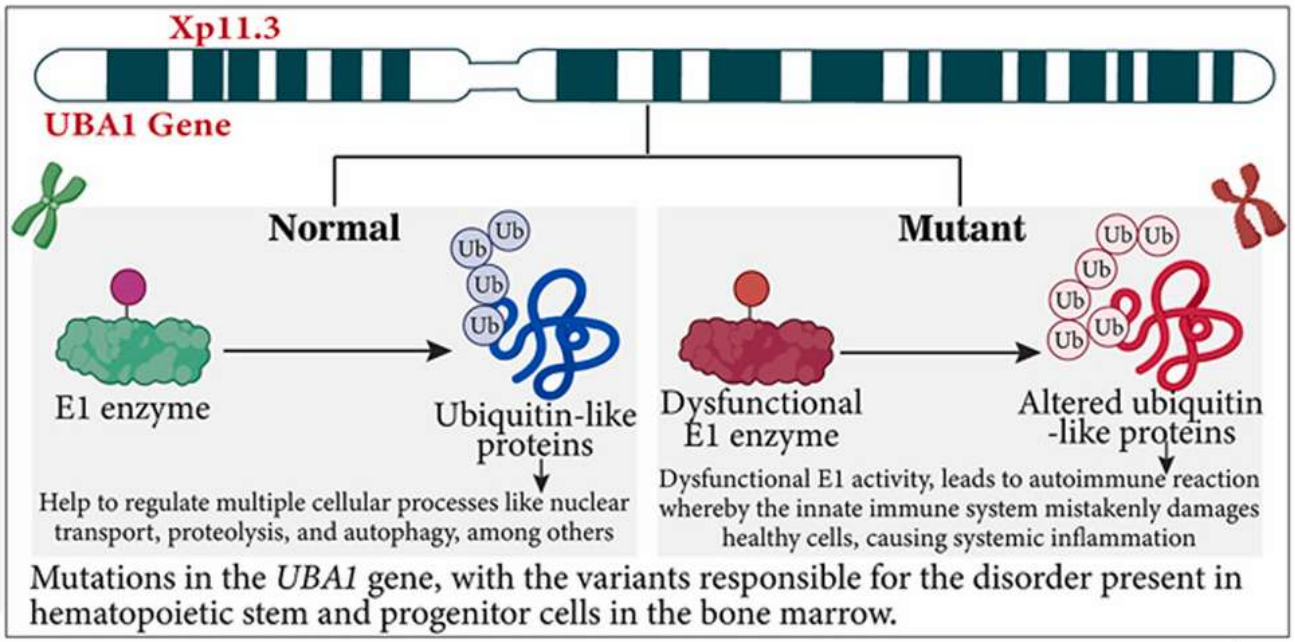
VEXAS SYNDROME – WHAT IS IT?

- Adult onset autoinflammatory syndrome caused by somatic mutations in the UBA1 gene in hematopoietic stem cells

VACUOLES
E1 ENZYME
X LINKED
AUTOINFLAMMATORY
SOMATIC

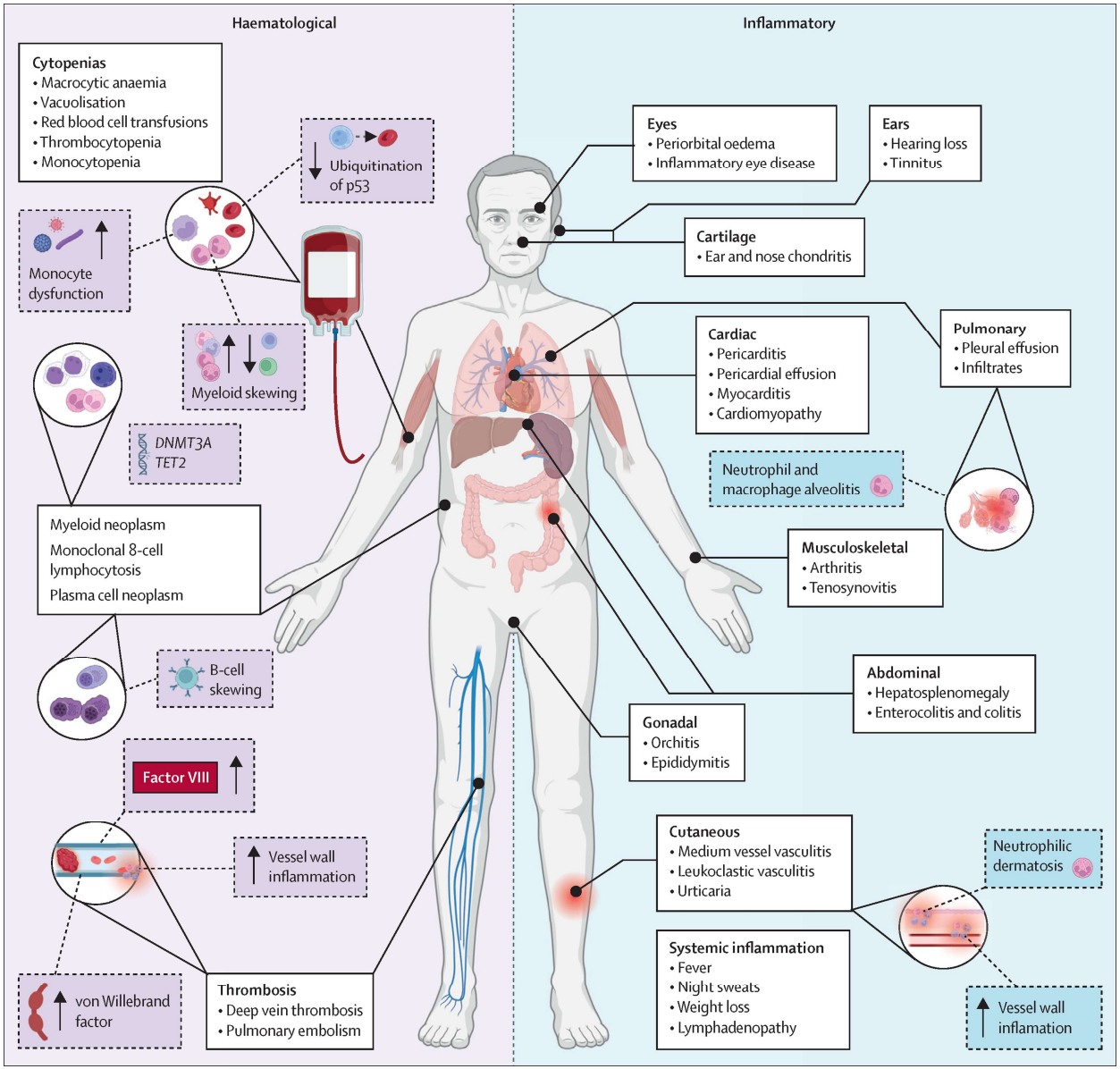
GENETIC/MOLECULAR BASIS

- VEXAS syndrome is driven by **acquired (somatic)** mutations in UBA1
- X-linked so predominantly affects men over age 50



Mutations in the *UBA1* gene, with the variants responsible for the disorder present in hematopoietic stem and progenitor cells in the bone marrow.

Singh and Chaudhary 2025


Haematological
Inflammatory
Cytopenias
• Macrocytic anaemia
• Vacuolisation
• Red blood cell transfusions
• Thrombocytopenia
• Monocytopenia
Ubiquitination of p53
Monocyte dysfunction
Myeloid skewing
DNMT3A
TET2
Myeloid neoplasm
Monoclonal B-cell lymphocytosis
Plasma cell neoplasm
B-cell skewing
Factor VIII
Vessel wall inflammation
von Willebrand factor
Thrombosis
• Deep vein thrombosis
• Pulmonary embolism
Eyes
• Periorbital oedema
• Inflammatory eye disease
Ears
• Hearing loss
• Tinnitus
Cartilage
• Ear and nose chondritis
Cardiac
• Pericarditis
• Pericardial effusion
• Myocarditis
• Cardiomyopathy
Pulmonary
• Pleural effusion
• Infiltrates
Neutrophil and macrophage alveolitis
Musculoskeletal
• Arthritis
• Tenosynovitis
Abdominal
• Hepatosplenomegaly
• Enterocolitis and colitis
Gonadal
• Orchitis
• Epididymitis
Cutaneous
• Medium vessel vasculitis
• Leukoclastic vasculitis
• Urticaria
Neutrophilic dermatosis
Systemic inflammation
• Fever
• Night sweats
• Weight loss
• Lymphadenopathy
Vessel wall inflamation

Lancet 2026

KEY CLINICAL FEATURES

Hematologic Involvement

- Cytopenias
- Myelodysplastic syndromes

Inflammatory Features

- Refractory fevers
- Relapsing polychondritis (especially of ears and nose)
- Persistent skin rashes such as neutrophilic dermatoses or vasculitis.

Organ-Specific Involvement

- Pulmonary infiltrates
- Recurrent pneumonia
- Chondritis of the respiratory tract

DIAGNOSIS AND PROGNOSIS

- Genetic confirmation of pathogenic UBA1 variants
  - Targeted sequencing of exon 3 or full gene sequencing
- Bone marrow biopsy
  - Hypercellularity for age, left shifted granulopoiesis, cytoplasmic vacuolization of myeloid + erythroid precursors

- Prognosis poor with 30-50% mortality at 5 years
  - Deaths related to severe inflammation, infection, bone marrow failure and treatment complications

COGNITIVE DYSFUNCTION IN VEXAS

“Brain fog”

VEXAS Pathways to Cognitive Impairment

01

Systemic inflammation

Chronic cytokine burden primes CNS effects

02

Neuroinflammation

Immune activation within brain networks

03

Endothelial dysfunction

Vascular injury signals microvascular risk

04

Microvascular injury

Small-vessel brain injury accumulates

05

Cytopenias worsen hypoxia, repeat cycle

Cognitive Dysfunction

- Anywhere from 6-8% of patients to 30% and above
- Largest systematic study from French VEXAS registry – 30% of patients have neurological involvement
  - Encephalopathy
  - Lacunar cerebral infarcts
  - Posterior reversible encephalopathy syndrome

Working Memory/Attention Deficits

Reduced ability to hold and manipulate information, impacting multitasking and complex daily tasks.

Processing Speed Impairment

Slowed cognition and response, reducing efficiency in reading, decision-making, and work pace.

Executive Function Challenges

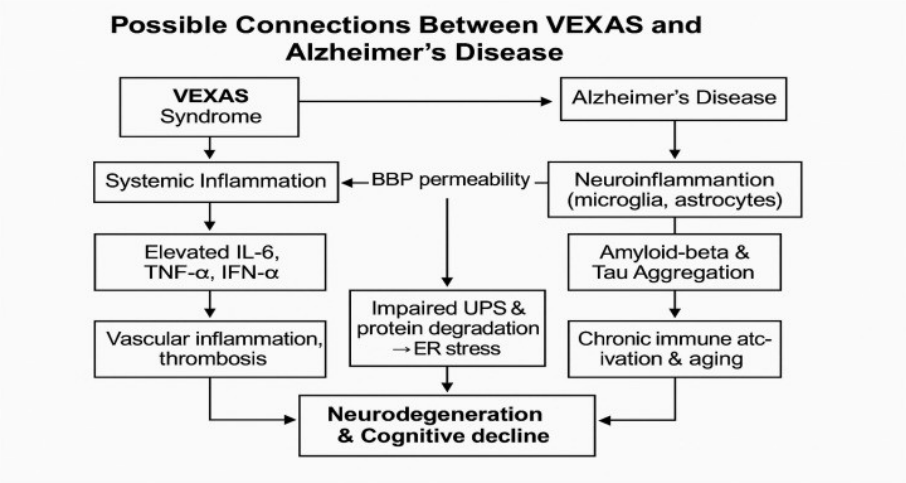
Difficulties with planning and cognitive flexibility, affecting organization and adapting to change.

Language

VEXAS VERSUS MAJOR NEUROCOGNITIVE DISORDERS

SIMILARITIES

Mechanism
- Both are inflammatory



Sowa 2025

Clinical Presentation

Executive Dysfunction

Planning and organization difficulties complicate decisions and multi-step tasks in both.

Memory Lapses

Short-term recall issues occur in both, disrupting daily functioning and routine tasks.

Slowed Processing

Reduced speed on cognitive tasks affects response time and communication across disorders.

Testing Overlap

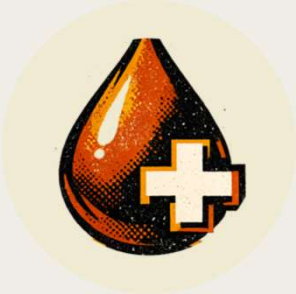
Standard measures can look similar, requiring comprehensive evaluation for differentiation.

Feature	VEXAS Syndrome	Major Neurocognitive Disorders
Onset	**Acute or Subacute** (days to weeks)	**Insidious** (gradual over years)
Progression	Fluctuating; often follows systemic "flares"	Steadily progressive decline
Primary Driver	**Systemic Inflammation** (Cytokine storm)	**Neurodegeneration** (Protein buildup)
Demographics	Primarily **men over age 50**	All genders; risk increases with age (65+)
Inflammatory Markers	**Very High** (ESR, CRP, Ferritin)	Normal or mildly/modestly elevated
Hematology	**Macrocytic anemia** and bone marrow vacuoles	Typically no specific blood abnormalities
Systemic Symptoms	**Fever, skin rashes, chondritis**, lung issues	Generally absent
MRI Findings	Acute lesions (infarcts, PRES, or white matter swelling)	**Brain atrophy** (shrinkage) in specific regions
Genetic Cause	Somatic **UBA1 mutations**	APOE ε4 (risk) or APP/PSEN (familial)
Response to Treatment	**Often reversible** with steroids/immunosuppressants	Minimal/symptomatic response to drugs

MANAGEMENT AND PROGNOSIS

Immunosuppressive Therapies

- Corticosteroids
- JAK inhibitors
- Targeted therapies (IL-6)



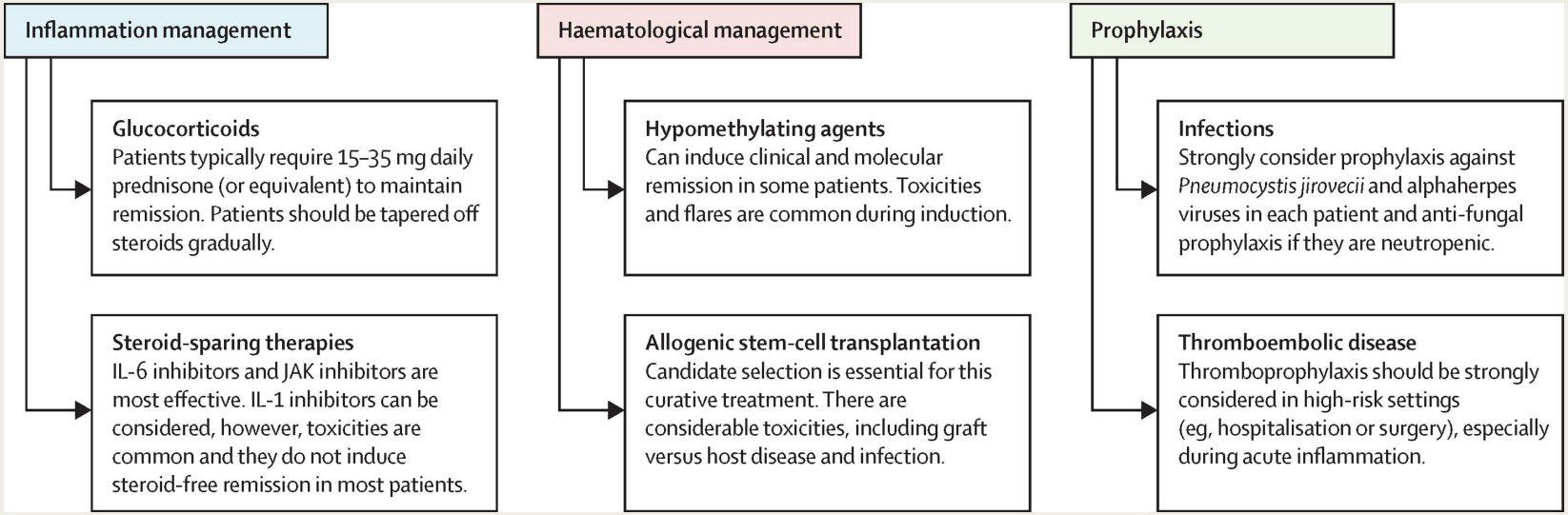
Hematologic Interventions

- Transfusion supports
- Hypomethylation: azacitidine

Allogeneic hematopoietic stem cell transplantation remains only curative option

Multidisciplinary Care & Early Diagnosis

- Collaborative approach involving rheumatology, hematology, and other specialties


Inflammation management
Glucocorticoids
Patients typically require 15–35 mg daily prednisone (or equivalent) to maintain remission. Patients should be tapered off steroids gradually.
Steroid-sparing therapies
IL-6 inhibitors and JAK inhibitors are most effective. IL-1 inhibitors can be considered, however, toxicities are common and they do not induce steroid-free remission in most patients.
Haematological management
Hypomethylating agents
Can induce clinical and molecular remission in some patients. Toxicities and flares are common during induction.
Allogenic stem-cell transplantation
Candidate selection is essential for this curative treatment. There are considerable toxicities, including graft versus host disease and infection.
Prophylaxis
Infections
Strongly consider prophylaxis against *Pneumocystis jirovecii* and alphaherpes viruses in each patient and anti-fungal prophylaxis if they are neutropenic.
Thromboembolic disease
Thromboprophylaxis should be strongly considered in high-risk settings (eg, hospitalisation or surgery), especially during acute inflammation.

Managing Cognitive Dysfunction in VEXAS

Optimize control of systemic inflammation

Prioritize disease-directed therapy to reduce inflammatory burden and downstream neurocognitive impact.

Symptomatic neurocognitive therapies

Address attention, mood, sleep, and functional deficits with targeted interventions and specialist input.

Supportive care + longitudinal reassessment

Integrate cognitive rehabilitation and regular monitoring to adapt the plan as symptoms and disease evolve.

CASE

- Underwent extensive testing
  - repeat bone marrow biopsy – hemophagocytosis, no granulocyte vacuolation
  - Myeloid panel testing and local UBA1 testing on bone marrow sample negative
  - Thoracic lymph node biopsy negative
- The patient was eventually started on prednisone and azacitadine
- Some evidence of reduction in inflammatory markers and cognitive/functional recovery is pending

SUMMARY

• **The "Red Flags“**
- In an older man, the combination of **rapid** cognitive decline, **fevers/inflammatory symptoms**, and a high **MCV** (macrocytic anemia) should immediately raise suspicion for VEXAS rather than a primary dementia

• **Treatability**
- Unlike neurodegenerative dementias, which are currently incurable, VEXAS-associated cognitive changes can significantly improve or even resolve with targeted anti-inflammatory therapy.

• **Testing**
- Genetic testing for the UBA1 gene is the definitive way to confirm VEXAS, while dementia is often diagnosed through clinical patterns and biomarkers (like p-tau)

• **Interdisciplinary Approach**
- Involvement of Rheumatology and Hematology +/- Neurology

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Q & A

Comments...