Clinical Characteristics and Phenotypic Plasticity of Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) Syndrome: A Systematic Review and Meta-analysis

Daniela Vulpe, Xiang Zhu, MS, Jane Gibson, PhD and Hatem Kaseb, MD, PhD, MPH
University of Central Florida College of Medicine, Orlando, FL, USA.

FLORIDA SOCIETY OF PATHOLOGISTS

UCF College of Medicine
UNIVERSITY OF CENTRAL FLORIDA

Introduction

- Vacuoles, E1 enzyme, X linked, autoinflammatory, somatic (VEXAS) syndrome is an adult onset autoinflammatory condition first described in 2020 by Beck et al. [1]
- The syndrome is caused by somatic mutations in the *UBA1* gene and is X-linked recessive; Thus, it mostly presents in males with rare cases observed in females.[2]
- Most reported genetic mutations are a substitution of Methionine-41 (p.Met41) contributing to a range of disease manifestation and severity levels. [1]
- Patients present with hematological disease and inflammatory syndrome (Figure 1).
- This is an adults-onset fatal disease that may present as myelodysplastic syndrome, aplastic anemia or multiple myeloma, but characterized by fevers, leucopenia, vacuoles in bone marrow cells, dysplastic bone marrow, pulmonary inflammation, chondritis, and vasculitis. [1]
- Herein, we conduct a systematic review paired with a meta-analysis of VEXAS Syndrome symptoms.

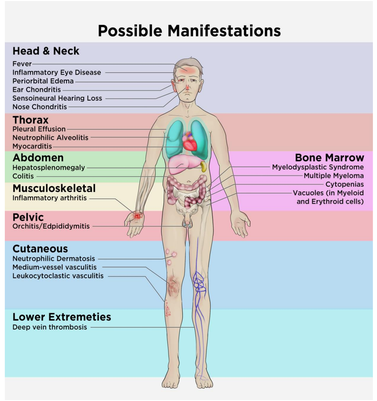
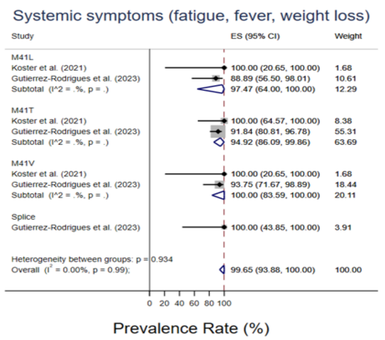


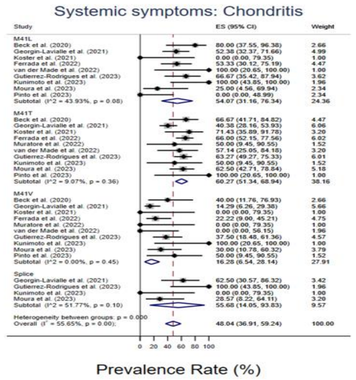
Figure 1. Possible VEXAS symptoms

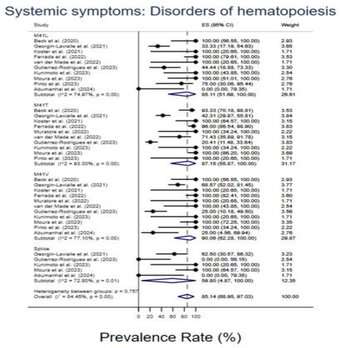
Methods

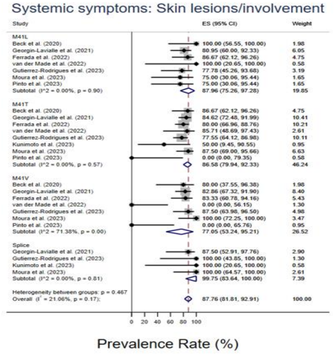
- The sources for the literature review were primarily located through the PubMed database using a specific search string.
- The prevalence rate of each outcome syndrome from the individual studies was transformed into a quantity using Freeman-Tukey Double Arcsine Transformation. The pooled prevalence rate was estimated as the back-transform of the weighted average of the transformed prevalence rates using random effect models and Laird's weight method. Forest plots were constructed to show the point estimates in each study in relation to the summary pooled estimate of overall prevalence rates with subtotals organized on mutation type. The width of the point estimates in the Forest plots corresponded to the assigned weight of the study.
- Heterogeneity among the studies was assessed using Cochran's "Q" test (with tau2 and a P-value) and I 2 statistics.
- The robustness of the meta-analysis to publication bias was assessed by using funnel plots. All the analyses were performed using STATA MP 15.1 (STATA Corp LP, College Station, Texas, United States).

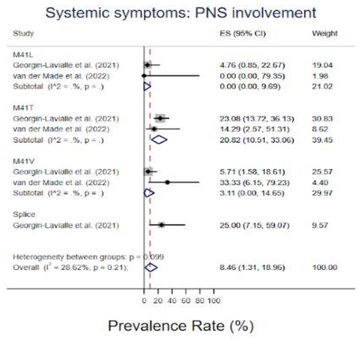
Results











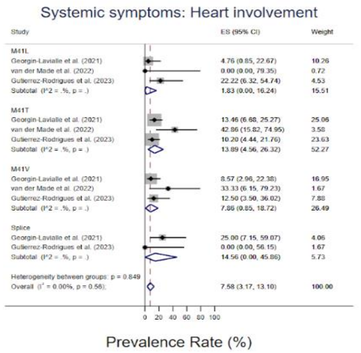


Figure 2. Forest plots showing symptoms based on the three common mutations.

Results

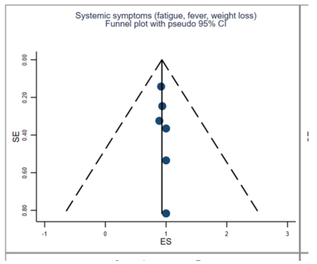


Figure 3. Systemic symptoms funnel plot

- 11 studies (n = 11) were included in the meta-analysis.
- Select forest plots of the analysis are presented in Figure 2.
- Systemic symptoms are the most common symptoms in VEXAS syndrome The pooled prevalence is 100% with no significant heterogeneity between groups (p=0.934), indicating a strong consensus among all studies.
- Furthermore, the funnel plot shows no major publication bias. (Figure 3)
- There is moderate evidence suggesting chondritis is prevalent in VEXAS Syndrome, especially in the M41L mutation group.
- Disorders of hematopoiesis are consistently prevalent across all mutations/groups with M41V having highest prevalence.
- GI, Heart and PNS symptoms were the least common symptoms in VEXAS syndrome
- Skin involvement is high among all studies (87.76%) with overall low heterogeneity suggesting that all results are consistent across studies. However, there was high heterogeneity in the M41V group which prompts further exploration.
- The pooled prevalence mortality was approximately 20%
- The most common of the three treatment options was Steroids

Conclusions

- VEXAS syndrome is a recently defined disease falling within the category of "hematoinflammatory diseases."; several unknown aspects concerning the disease still exists. These include: the role of additional mutations in disease progression, risk stratification, the full genetic mutational spectrum of the disease and the optimal management/surveillance approach for these patients.
- Our study analyzed the symptoms associated with the most common *UBA1* mutations in VEXAS Syndrome.

References

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in uba1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383(27):2628-2638. doi: 10.1056/NEJMoa2026834.
2. Beck DB, Bodian DL, Shah V, et al. Estimated prevalence and clinical manifestations of uba1 variants associated with vexas syndrome in a clinical population. JAMA. 2023;329(4):318-324. doi: 10.1001/jama.2022.24836.