PATIENT GUIDE | VEROS HEALTH | IMMUNOe HEALTH & RESEARCH

Understanding Hereditary Angioedema, Normal C1e

Hereditary Angioedema with Normal C1e Inhibitor (HAE-nC1eINH)

SCAN FOR FULL GUIDE

THE IMMUNE CONNECTION

HAE Normal C1e is driven by the same overactive bradykinin pathway seen in other forms of hereditary angioedema — even though standard C1e inhibitor testing comes back normal. At Veros, our immunology team looks past that normal lab value to identify and manage the pathway actually driving your swelling episodes.

WHAT IS HAE NORMAL C1E?

Hereditary angioedema (HAE) causes episodes of swelling under the skin and in the gut or airway. In HAE types 1 and 2, blood tests show low or malfunctioning C1e inhibitor. In HAE Normal C1e, that same protein tests normal — but researchers believe the underlying problem is still too much bradykinin, a substance that widens blood vessels and makes it leak fluid into surrounding tissue. HAE Normal C1e tends to run in families, is more common in women, and is often triggered or worsened by estrogen, though men can have it too.

DIAGNOSIS

HAE Normal C1e is often a diagnosis of exclusion: C4, C1e inhibitor level, and C1e inhibitor function all test normal. Genetic testing may identify a mutation (in genes such as KNG1, plasminogen, or factor XII), though most patients don't have an identified mutation yet. Ruling out histamine- or mast-cell-driven angioedema is an important step, and how you respond to bradykinin-pathway treatment can help confirm the diagnosis.

GENETIC SUBTYPES

Five subtypes are currently recognized, based on the gene involved. Most patients fall into the "Unknown" category, where no mutation has been identified yet — this doesn't change the diagnosis, but genetic subtype can help guide treatment choice.

- **HAE-FXII (factor XII)**— most common identified mutation in Europe; rare in the US
- **HAE-PLG (plasminogen)**— often marked by prominent tongue swelling
- **HAE-ANGPT1 (angiopoietin-1)**— disrupts a receptor that normally limits vessel leakiness
- **HAE-KNG1 (kininogen-1)**
- **HAE-Unknown**— the majority of patients; no identified mutation yet

COMMON SYMPTOMS

- Swelling of the face, lips, or tongue — the most frequent attack sites, more so than in HAE types 1/2
- Hand, foot, or limb swelling
- Abdominal swelling with cramping, nausea, or vomiting
- No hives and no itching — unlike a typical allergic reaction
- Little or no improvement with antihistamines, steroids, or epinephrine
- Attacks build over hours and can last 2-5 days if untreated
- Warning signs — tingling, fatigue, headache — before visible swelling
- Often more disease-free intervals, and later symptom onset (late teens/early adulthood), compared to HAE types 1/2

Emergency Warning Signs: Throat or tongue swelling, trouble breathing or swallowing, or a voice change can signal airway swelling. Go to the ER or call 911 right away.

HOW WE EVALUATE & TREAT AT VEROS

Lab workup:
C4, C1e inhibitor level and function, and complement studies to rule out HAE types 1 and 2.

Genetic testing:
Screening for known bradykinin-pathway gene changes (FXII, PLG, ANGPT1, KNG1) when clinically indicated.

Trigger review:
Hormonal history, medications, and a symptom diary to map your personal pattern.

Action plan:
A written plan covering early-warning signs, on-demand treatment, and when to seek emergency care.

BIOLOGIC & TARGETED THERAPY

Because HAE Normal C1e involves the same bradykinin pathway as HAE types 1 and 2, some patients respond to on-demand or preventive therapies developed for those types — even with a normal C1e inhibitor level. Most of these options are not officially approved for HAE Normal C1e, so your allergist/immunologist will review eligibility, evidence, and insurance coverage with you before starting any treatment.

HORMONES, DIET & PACING

Estrogen is one of the strongest known triggers, particularly in the HAE-FXII subtype — in one cohort, stopping combined estrogen-progestin birth control resolved attacks in 97% of HAE-FXII patients. Talk with your care team before starting or changing birth control, hormone therapy, or if you're planning a pregnancy. Stress management and consistent sleep may help reduce attack frequency for some patients. Always consult your Veros provider before starting any new supplement or changing a medication dose.

HAE AND CVID

CVID is a genuine overlap worth knowing about:
A small, emerging number of case reports describe patients with both — including a 2026 case identifying shared HLA gene variants, though this is still preliminary. Separately, some CVID patients on IVIG have low C1e inhibitor contributing to infusion reactions; C1e-inhibitor replacement (the same class used in HAE) has shown early promise here, in research from IMMUNOe's own research centers.

WHY VEROS HEALTH?

- v 30+ years of immune expertise — IMMUNOe Health & Research
- v Multi-specialty team experienced with rare bradykinin disorders
- v Biologic and targeted on-demand therapy available on-site
- v Coordinated care for hormone-related triggers and co-occurring conditions
- v Personalized action plans and ER-ready documentation