

Laryngeal Edema in a Child with Hereditary Angioedema with Normal C1 Inhibitor



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Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by nonpitting edema of the deep dermis, subcutaneous, or submucosal tissue. Edema typically involves the extremities, intestinal tract, face, or upper airway. The angioedema is mediated by bradykinin and therefore does not respond to antihistamines, steroids, and epinephrine. The onset of symptoms is usually during childhood and frequently worsens around puberty. This can be a life-threatening condition due to the risk of upper airway obstruction. HAE is due to a mutation in the gene that encodes C1 inhibitor, resulting in a reduction of C1 inhibitor (type 1) or present but dysfunctional protein (type 2). In 2000, a new classification of HAE with normal complement was described (HAE-nmlC1-INH).¹

An 11-year-old girl presented with a 3-year history of recurrent episodes of edema of the face, tongue, and lips that were unresponsive to high-dose antihistamines and epinephrine. Family history was remarkable for HAE-nmlC1-INH in

her mother. During one of her acute attacks, she presented to the emergency department with difficulty breathing and experiencing rapidly evolving facial and tongue swelling in the setting of a sensation of throat closing. The patient denied associated itchiness, and no signs of urticaria were seen. Antihistamines and epinephrine were used without improvement of her symptoms. Laboratory workup showed a C4 value of 24.3 mg/dL (normal, 16.5-38.0 mg/dL), C1-Inhibitor level of 23 mg/dL (normal, 21-39 mg/dL), and function 102% (normal, $\geq 40\%$). Computed tomography (CT) of the neck (Figure 1, A) at the time of the symptoms is presented comparatively to her baseline CT (Figure 1, B). In Figure 1, A, findings revealed diffuse retropharyngeal soft tissue swelling extending from C1 to C5, causing a significant narrowing of the pharyngeal airway. Mild swelling of the base of the tongue and glottis is also seen. Figure 1, B, demonstrates her normal pharyngeal airway dimensions.

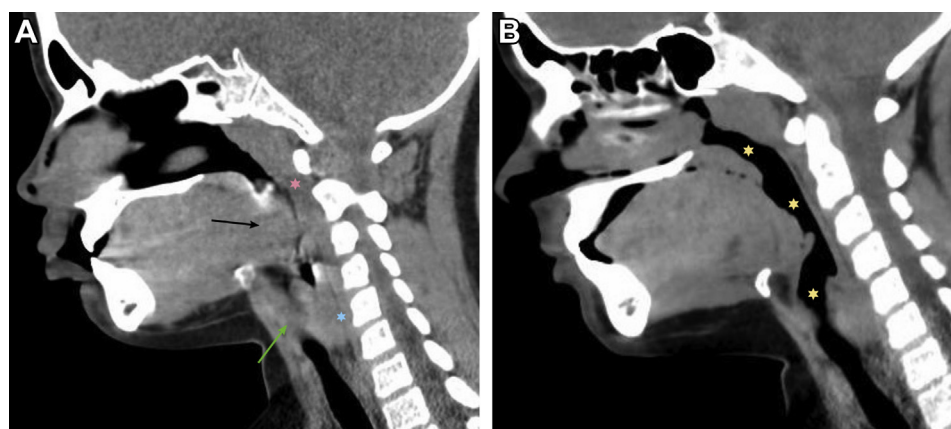


FIGURE 1. Midline sagittal non-contrast enhanced computed tomography of the neck, A and B (baseline). A, Comparatively, with a normal baseline study (B), findings revealed a mild enlargement of the base of the tongue (black arrow), glottis (green arrow), and diffuse retropharyngeal soft tissue thickening extending from C1 (pink star) to C5 (blue star), causing a significant narrowing of the pharyngeal airway. B, Normal pharyngeal airway dimensions (yellow stars).

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This case illustrates the diagnosis of HAE-nmlC1-INH. Even though genetic testing was cost prohibitive, the patient was diagnosed with HAE-nmlC1-INH based on a detailed medical history and clinical features, normal laboratory values on repeated occasions, and positive family history of HAE-nmlC1-INH. After the family declined prophylactic therapy with androgens, plasma-derived C1-INH was started. The patient continued having exacerbations that were triggered by stress and onset of puberty. Her acute attacks were successfully managed with on-demand ecallantide. However, symptoms still recurred every 2 weeks, prompting a trial of prophylactic tranexamic acid (25 mg/kg/day) and the use of on-demand icatibant. Three months after therapy, the patient was tolerating tranexamic acid with no further angioedema attacks or need of on-demand therapy.

HAE-nmlC1-INH was initially thought to be due to a gain of function mutation in Factor XII protease (Hageman factor). More recently 2 different mutations have been described such as angiotensinogen and plasminogen (PLG), but the majority of cases are still classified as HAE because of an unknown origin.² The diagnosis is considered in patients with the characteristic clinical manifestations, a strong family history, normal complements (C1, C4), and C1 inhibitor levels with response to medications typically used to treat type 1 and 2 HAE. Genetic testing for

factor XII mutation and ANGP1 should become part of the routine workup evaluation. Also, medications that may trigger angioedema such as angiotensin-converting enzyme and nonsteroidal anti-inflammatory drugs should be ruled out.

The treatment of pediatric HAE is challenging due to limited Food and Drug Administration–approved therapies in the pediatric population under age 12. Antifibrinolytics have been used in the management of HAE because of its effect on the PLG activation process by decreasing bradykinin generation. There are no clinical trials of tranexamic acid in patients with HAE-nmlC1-INH. This case demonstrates the effectiveness of tranexamic acid in preventing attacks in HAE-nmlC1-INH in a pediatric patient who failed plasma-derived C1-INH therapies. More studies need to be conducted regarding the pathophysiology of HAE-nmlC1-INH along with placebo-controlled clinical trials in children to elucidate the medical management of this condition.

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