



Letter

Blindness, tetraspasticity, and other signs of irreversible brain damage in hereditary angioedema

Hereditary angioedema (HAE) caused by a genetic C1 esterase inhibitor (C1-INH) deficiency (HAE-C1-INH) is clinically characterized by recurrent skin swellings, abdominal pain attacks, and, more rarely but potentially life-threatening, upper airway obstruction (supraglottic edema, laryngeal attacks). Cerebral symptoms are rare in HAE-C1-INH.^{1,2} HAE-C1-INH attacks, including laryngeal attacks, usually occur unpredictably. They may reach their maximal intensity usually 1 to 12 hours after onset, reflecting some variability in the development time.³ Patients with undiagnosed HAE-C1-INH are particularly at risk to asphyxiate.⁴

We describe 2 patients with HAE-C1-INH who survived severe laryngeal attacks but, because of hypoxic brain damage, had irreversible sequelae, including central blindness and tetraspasticity.

Patient 1 was a 29-year-old man with approximately 3 undiagnosed hand and foot swellings on average per year from 14 to 18 years of age. He had no family history of angioedema. At 18 years of age, the patient attended a tattoo studio for tongue piercing. A few minutes after piercing, severe tongue swelling started followed by an upper airway obstruction. Ten minutes later the patient lost consciousness and stopped breathing. At that time, an ambulance arrived and cricothyrotomy was immediately performed, followed by artificial respiration. During a subsequent stay in an intensive care unit, hypoxic brain damage and HAE-C1-INH type 1 were diagnosed. In plasma, C1-INH activity was less than 1% (reference range, 70%–130%), the C1-INH protein level was less than 4.8 mg/dL (reference range, 15.4–33.8 mg/dL), and the C4 level was less than 4.8 mg/dL (reference range, 16.4–31.3 mg/dL). Sequelae of the brain damage were cortical blindness, tetraspasticity with a dystonic component, and an organic delusional disorder with hearing voices and various organic intellectual performance deficits, motoric deficits, and changes in personality. The patient required a wheelchair. During the following 11 years to the present, the patient has been living in a nursing home. Since the age of 18 years, the patient had 7 further skin swellings, including 2 facial swellings and 1 scrotal edema. He also had approximately 5 abdominal attacks. Skin swellings and abdominal attacks were controlled by on-demand treatment with plasma-derived C1-INH concentrate or icatibant.

Patient 2 was a 20 year-old Syrian refugee with known HAE-C1-INH who had more than 100 skin swellings (hands, feet, face, scrotum), tongue swellings, abdominal attacks, partly with vomiting, and 1 laryngeal attack since the age of 8 years. The attacks lasted usually 2 to 3 days. The patient had no family history of angioedema. At the age of 19 years, the patient reached Germany and stayed in various refugee camps. One night he developed increasing dysphagia and severe dyspnea within 30 minutes after a previous hand swelling 1 day earlier. The patient

lost consciousness, and nearly at the same time breathing stopped and the pulse was no longer palpable. In the ambulance, the patient immediately received oxygen, heart massage, and defibrillation and was transported to the next intensive care unit, where a hypoxemic brain damage was diagnosed. The cortex, brainstem, and cerebellum were damaged. Magnetic resonance imaging revealed damage of the basal ganglia and cortex (Fig 1). The irreversible sequelae of the brain damage included cerebral cortical blindness, tetraspasticity, and athetotic movement disorders. A diagnosis of HAE-C1-INH type 1 was confirmed by laboratory results (C1-INH activity, 5.7% [reference range, 70%–130%]; C1-INH protein level, 2.9 mg/dL [reference range, 17–44 mg/dL]; C4 level, 3.7 mg/dL [reference range, 10–40 mg/dL]; and C1q level, 22 mg/dL [reference range, 10–25 mg/dL]). In the following 15 months, the patient had approximately 9 skin swellings, 6 abdominal attacks, and 2 laryngeal attacks and was treated on demand with plasma-derived C1-INH concentrate or icatibant.

Both patients had a laryngeal attack with complete upper airway obstruction as a symptom of HAE-C1-INH and lost consciousness because of hypoxemia before any treatment started. Reanimation was successful so that at least the lives of the patients could be saved. We assume that in both patients the laryngeal attacks were developing so rapidly that reanimation came too late to avoid the hypoxic brain damage. At the time of the described attacks, the diagnosis of HAE-C1-INH was unknown in patient 1 and known in patient 2.

Laryngeal attacks represent only approximately 1% of attacks in patients with HAE-C1-INH. The course of laryngeal attacks may include a predyspnea phase, a dyspnea phase, and a loss-of-consciousness phase.⁴ Complete recovery and death by asphyxiation have been reported in treated and untreated patients with HAE-C1-INH. Complete recovery without any residual impairment was reported for 324 untreated laryngeal attacks in 24 patients.⁵ Furthermore, complete recovery was reported in numerous laryngeal attacks of many patients treated on demand with various drugs.^{5–7} Death by asphyxiation in untreated, delayed treated, or inadequately treated patients has been reported many times and in numerous patients. One case was already mentioned in one of the earliest descriptions of HAE.⁸

We report a third kind of outcome, survivors of far advanced laryngeal attacks having irreversible disabilities as sequelae of brain damage after cardiac arrest and hypoxemia. Until now there have been no reports of patients with HAE-C1-INH who have survived a severe laryngeal attack that required reanimation measures and who subsequently remained permanently disabled because of hypoxic brain damage. The short course of the laryngeal attacks in the patients described here underlines the necessity of an early

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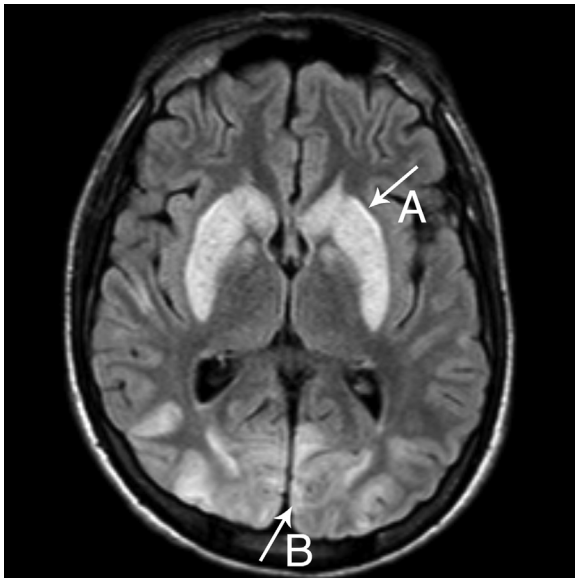


Figure 1. Magnetic resonance imaging of patient 2. Signs of diffuse hypoxic ischemia. Fluid-attenuated inversion recovery sequence: high-signal intensity (damaged tissue) in basal ganglia (caudate nucleus, striatum) (arrow A) and occipital lobe (visual cortex) (arrow B).

diagnosis, a disease documentation, and an optimal treatment plan for laryngeal attacks in patients with HAE-C1-INH, including treatment with drugs that can rapidly counter the laryngeal attack.^{9,10}

Konrad Bork, MD*
 Randolph Brehler, MD†
 Günther Witzke, PhD*
 Stephan Boor, MD‡
 Wolf Heineke, MD§
 Jochen Hardt, PhD||

*Department of Dermatology
 Johannes Gutenberg University
 Mainz, Germany

†Department of Dermatology
 University Hospital
 Münster, Germany

‡Department of Neuroradiology
 Johannes Gutenberg University
 Mainz, Germany

§Department of Neurology
 Clinic Ibbenbüren
 Ibbenbüren, Germany

||Department of Medical Psychology and Medical Sociology
 Johannes Gutenberg University
 Mainz, Germany

bork@hautklinik.klinik.uni-mainz.de

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