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# Abdominal hereditary angio-oedema caught on magnetic resonance imaging

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## SUMMARY

A 17-year-old woman presented with a 3-year history of recurrent, severe abdominal pain with spontaneous resolution within a few days. An ultrasound revealed nothing more than free fluid within the pelvis. An MRI of the small bowel was done within 24 hours of abdominal pain onset, which revealed extensive submucosal oedema associated with moderate volume ascites. A repeat MRI of the small bowel after 72 hours showed near-complete resolution of these changes. Checking C1 inhibitor levels confirmed a diagnosis of hereditary angio-oedema with an abdominal presentation. This is a rare cause of recurrent abdominal pain and, to our knowledge, the first case in which MR images have been obtained during and after an acute attack.

## BACKGROUND

Hereditary angio-oedema (HAE) is a rare condition which normally presents with recurrent swelling of the lips, extremities and pharynx. Abdominal angio-oedema, which presents typically with abdominal pain and distension, is often missed due to the large number of differentials of acute abdominal pain. The average time from first presentation to diagnosis in HAE has been reported as 8–10 years.

We report a case of a 17-year-old woman presenting with recurrent admissions to hospital with acute abdominal pain, who was later diagnosed with HAE. She had no extra-abdominal symptoms of the disease other than ankle swelling. An MRI of the small bowel was performed during an acute attack of pain. This demonstrated ascites and small bowel submucosal oedema, in what may be the first example of abdominal angio-oedema visualised on MRI. These findings spontaneously resolved on repeat imaging 72 hours later.

## CASE REPORT

A 17-year-old Caucasian woman presented to the medical take with a 3-year history of recurrent, severe abdominal pain. The pain was characterised by gradual onset lower abdominal discomfort, with rapid progression to severe diffuse colicky pain. It was associated with intermittent vomiting, which did not relieve the pain. She also reported swelling of her ankles, anorexia and constipation. She denied fever or breathlessness. She had seven episodes of this stereotyped abdominal pain in the past and was previously admitted under the surgical team—her symptoms would resolve spontaneously over 1–5 days with no formal diagnosis done.

She took naproxen on occasion for mittelschmerz (unilateral abdominal pain associated with ovulation). She had severe reactions to insect bites and was intolerant to strawberries. Her father had a history of common variable immunodeficiency.

## INVESTIGATIONS

Initial blood on the latest admission was reported as follows: CRP 14 mg/L, white cell count  $21 \times 10^9/L$ , platelets  $496 \times 10^9/L$ , with a normal haemoglobin and amylase. Three transabdominal ultrasounds were performed during an attack of pain during previous admissions and revealed free fluid in the pelvis with normal appearances of all other organs. An MRI scan of the small bowel was completed within 24 hours of presentation, which revealed extensive submucosal oedema of the jejunum with normal appearances of the mucosa and a moderate volume of ascites (figure 1). Repeat MRI scan of the small bowel was sought 72 hours later and confirmed near-complete resolution of these abnormalities, and only a small volume of ascites remained (figure 2).

## DIAGNOSIS AND MANAGEMENT

A clinical diagnosis of sporadic HAE was considered and confirmed by checking C4, C1 inhibitor level and function, which were low at 0.03 g/L (normal range (NR) 0.14–0.54 g/L), 0.06 g/L (NR 0.22–0.38 g/L) and 8% (NR 70%–130%), respectively. The patient was referred to an immunologist for further investigation and management. This is the first case of abdominal HAE to be caught on MRI during an acute attack.

## OUTCOME AND FOLLOW-UP

The patient has been referred to a tertiary immunology service. She was given an information letter outlining both her condition and suggested treatment if she presents to hospital with an acute flare in the future. She was given a supply of icatibant (a synthetic bradykinin 2 receptor antagonist) 30 mg subcutaneous injection as required and berinert (C1 inhibitor concentrate) 1000 units intravenous injection as required.

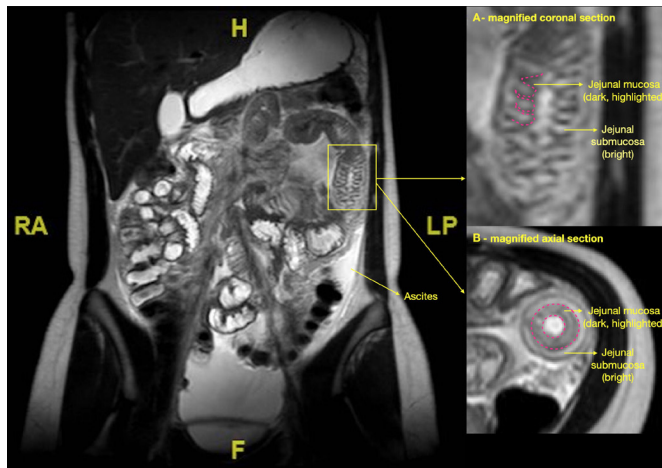
## DISCUSSION

HAE is a rare condition characterised by paroxysmal, prolonged attacks of swelling of the submucosal and cutaneous tissues, which resolve spontaneously within days. Laryngeal involvement may cause airway compromise and fatal asphyxiation. The prevalence is 1 in 50 000 and normally develops in childhood, with exacerbations most



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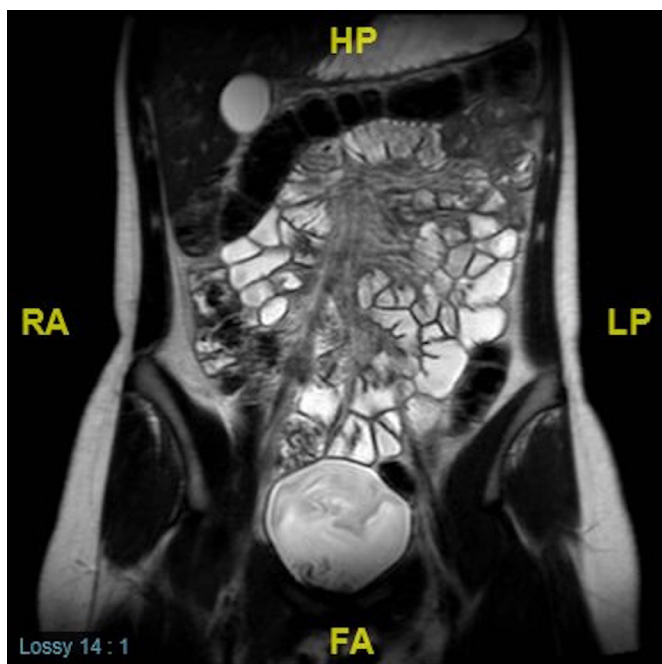


**Figure 1** Coronal T2-weighted MRI of small bowel within 24 hours of symptom onset showing ascites and submucosal oedema most prominent in the jejunum. (A) Magnified coronal section of jejunum. (B) Magnified axial section of jejunum.

frequently occurring during puberty. The time between onset of symptoms and diagnosis is variable, typically between 8 and 10 years.<sup>1</sup> In HAE, C1 inhibitor deficiency leads to inappropriate activation of complement and contact systems, resulting in uncontrolled bradykinin release and angio-oedema.<sup>2</sup>

Measurement of plasma C4 is a sensitive screening test for HAE, but C1 inhibitor level and function should be used to confirm the diagnosis.<sup>3</sup> Most cases are inherited in an autosomal dominant fashion, while approximately 25% of cases result from de novo mutations in the *SERPING1* gene.<sup>4</sup> Screening should be considered for anyone with a positive family history of HAE.

Multiple studies have evaluated the use of CT as an adjunct to aid diagnosis of abdominal HAE, with key findings revealing transient small bowel oedema and free fluid within the abdomen.<sup>5,6</sup> Abdominal ultrasound can also be used to visualise small bowel



**Figure 2** Coronal T2-weighted MRI of small bowel after 72 hours of symptom onset.

oedema. Although abdominal ultrasound is cheaper and more readily available than CT or MRI, submucosal thickening on ultrasound may not always be detected due to overlying bowel gas and may indicate other pathologies such as inflammation or haemorrhage.<sup>7,8</sup> This would indicate further imaging to rule out other pathologies. While findings on CT are mostly similar to those seen with MRI, using MRI avoids using ionising radiation and provides a superior evaluation of submucosal oedema with T2-weighted images.<sup>9</sup>

A brief literature search revealed several reported cases of HAE which initially presented with acute abdominal crises. Salas-Lozano *et al* (2014) report a case of a 33-year-old man who presented with acute abdominal pain and vomiting, was found to have free fluid and duodenal thickening on CT, and was later diagnosed with HAE.<sup>10</sup> Kasamatsu *et al* (2011) report a case of a 30-year-old woman with a similar presentation who responded to C1-INH concentrate.<sup>11</sup> Iwanami *et al* (2019) report a case of a 45-year-old woman who was diagnosed with HAE following recurrent admissions with an acute abdomen.<sup>12</sup> Oostergo *et al* (2013) report a case of a 48-year-old man who was diagnosed with HAE after initially presenting with an acute abdomen and having CT imaging.<sup>13</sup> Bin Hong *et al* (2013) report a similar case in a 21-year-old man who was again diagnosed with HAE following CT imaging.<sup>14</sup>

These cases describe mostly young patients investigated with CT during what would later be found to be acute flares of HAE, and there are reported cases of patients undergoing diagnostic laparoscopy and gastroscopy before being diagnosed. If readily available, MRI would be favourable as an initial cross-sectional imaging modality during acute attacks to avoid the risks of ionising radiation.

The International/Canadian Hereditary Angioedema Guidelines (2019) divide the management of HAE into on-demand treatment to halt acute attacks, short-term prophylaxis before a potential precipitant of an attack and long-term prophylaxis. Any medical, surgical or dental procedures may precipitate an attack in HAE, along with a number of patient-specific triggers. The on-demand treatment of choice in acute attacks is intravenous C1 inhibitor concentrate. Other treatment options include ecallantide, a kallikrein inhibitor, and icatibant, a synthetic bradykinin 2 receptor antagonist.<sup>15</sup> Fresh frozen plasma has also been used to treat acute attacks in the absence of any available drug therapy, as it contains small amounts of C1 inhibitor.<sup>16</sup>

Long-term prophylaxis may be necessary in patients with recurrent severe attacks. First-line options for long-term prophylaxis include subcutaneous C1 inhibitor concentrate, and lanadelumab, a monoclonal antibody against kallikrein. Attenuated androgens and antifibrinolytics such as tranexamic acid may also be of benefit in some patients.<sup>17</sup>

### Learning points

- ▶ Hereditary angio-oedema (HAE) is an important differential to consider in young patients with recurrent abdominal pain.
- ▶ A correct diagnosis will allow for rapid treatment and avoid unnecessary investigations in the future and avoid the inappropriate administration of epinephrine or corticosteroids in the case of anaphylactoid attacks.
- ▶ In patients with undiagnosed HAE presenting acutely with abdominal symptoms, imaging may be needed to obtain a diagnosis and rule out a surgical abdomen. Given that the average age of onset is young, MRI may be a better way to obtain radiological evidence of disease than CT in acute presentations suspicious for HAE.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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