Hereditary angioedema as a disease of different clinical courses and difficult diagnosis, particularly in children – a case report and literature review

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Hereditary angioedema (HAE) is a rare genetic disease with potentially fatal consequences [1]. Its estimated occurrence ranges from 1 : 10,000 to 1 : 50,000 [2]. A few types of HAE have been differentiated. HAE types 1 and 2 are most common, with depleted C1 inhibitor esterase (C1-INH) in serum or its dysfunction caused by a mutated SERPING1 gene [3]. The illness is mainly inherited through autosomal dominance, with 20–25% of cases caused by de novo mutation [4]. C1-INH, a member of the serpin group proteins, is a natural inhibitor of the initial phase of the complement cascade. Disrupting its concentration or function causes uncontrolled bradykinin production and accumulation, due to non-physiological activation of the complement system, the coagulation pathway, fibrinolysis and kallikrein cascade. When bound to its specific type 2 receptors, bradykinin induces a rapid increase in subcutaneous and submucosal blood vessel permeability, manifested as recurrent episodes of subcutaneous and submucosal tissue oedema.

This paper, basing on literature review from the last 5 years, presents 2 cases of HAE, with different clinical courses, where the condition was diagnosed at the age of 13 and 16 years. In both cases, the diagnosis was established many years after the first clinical symptoms, and in one, despite a positive family history.

A 16-year-old girl was admitted with oedema of the lips, hand and foot, which had recurred since 11 years of age: three times for oedema of the lips, and five times for oedema of the foot and hand. The asymmetrical oedemas were painless, developed over a few to 36 h and disappeared after one to four days; they lacked any obvious cause and were not accompanied by other symptoms. The girl’s mother had also experienced oedemas of the hands and feet. Previously, the girl had been treated with antihistamines and general steroids by her GP and the Emergency Department. However, following initial improvement, further use of treatment proved ineffective. At the age of 16, upon admission to the hospital, her general condition was good. Oedema of the upper lip and the cheeks was identified during the first hospitalisation, and a severe oedema of the right foot and hand during the second (generally she was 2 times in hospital). Basic laboratory test results were within norms (Table 1). Two tests performed over subsequent months revealed insufficient C4 complement in serum and reduced C1-INH activity and concentration (Table 1). A diagnosis of HAE type 1 was confirmed.

A 13-year-old girl was admitted with recurring abdominal pains, vomiting and diarrhoea. The history revealed an appendectomy at nine years of age and ultrasound examination indicated a large amount of the fluid in the retroperitoneal space. Since then, she had been hospitalized many times with abdominal pains, both in the Department of Surgery and in Paediatrics (6 times). At 10 years of age, an endoscopic examination of the digestive tract was performed in response to abdominal pains, vomiting and the presence of blood and mucus in the stools; although no macroscopic abnormalities were visible, histopathological examination identified inflammatory infiltrations which may be inflammatory bowel disease (IBD). Magnetic resonance imaging (MRI) with enterography did not identify any changes typical of IBD; however, based on the overall clinical picture, mesalazine was prescribed and continued until the age of 13 years. Despite treatment, the symptoms returned. Further tests were performed to exclude other causes.

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No bleeding from the digestive tract was observed after the girl turned 11, but the abdominal pains and vomiting recurred. In addition, ultrasound examinations of the abdominal cavity identified oedema of the intestinal wall and free fluid in the abdominal cavity. The symptoms and physical changes receded over a couple of days following the administration of restricted diet, analgesics, proton pump inhibitors and infusion fluids.

Two weeks before the most recent hospitalisation, at the age of 13, the patient reported vomiting, diarrhoea, and abdominal pains (VAS 10/10 points) which had significantly increased the day before arrival. On admission, although the overall condition of the girl was moderate, she was complaining of intense pains in the lower abdomen, which had continued without a break for a number of hours. Physical examination confirmed increased tension of the wall of the abdominal cavity and pain in the lower abdomen upon compression. The laboratory test results are given in Table 1. X-ray found no irregularities in the abdominal cavity. Ultrasound identified a thickening of the intestinal wall in the ileum and caecum region and a significant amount of the free fluid in the abdomi-
Table 2. Treatment and management in children with HAE as recommended by WAO/EAACI/HAWK 2018 [1, 10, 15]

| Management of podiatric HAE patients | Short-term prophylaxis (STP) | Long-term prophylaxis (LTP) |
|--------------------------------------|-----------------------------|-----------------------------|
| 1. Plasma-derived C1-INH i.v., 20 U/kg: | 1. Plasma-derived C1-INH i.v., 20 U/kg: | 1. Identification and elimination of triggering factors |
| – pdC1-INHBe (Berinert) \textsuperscript{a} \textsuperscript{b} | – pdC1-INHBe (Berinert) \textsuperscript{c} | |
| – pdC1-INHCl (Cinryze) \textsuperscript{b} | – pdC1-INHCl (Cinryze) | |
| 2. Recombinant human C1-INH (Rhucin, Ruconest) i.v., 50 units/kg \textsuperscript{c} | 2. Oral attenuated androgens (AAs) – can be used in the absence of pdC1-INH: | 2. Plasma-derived C1-INH pdC1-INHBe (Berinert) \textsuperscript{d} |
| \textsuperscript{c} | Danazol \textsuperscript{f} 2.5 to 10 mg/kg/day (maximum 600 mg daily) | \textsuperscript{f} i.v., 10-20 U/kg/dose 1–2×/week pdC1-INHCl (Cinryze) \textsuperscript{e} i.v., 1000 U 1–2×/week |
| 3. Ecallantide (Kalbitor) 30 mg s.c. \textsuperscript{e} \textsuperscript{f} | 3. FFP (fresh frozen plasma) i.v., 10 ml/kg – can be used in the absence of the above mentioned drugs | 4. Oral attenuated androgens (AAs) – are not considered for LTP in paediatrics prior to Tanner Stage V (danazol, stanozolol, oxandrolone), p.o. 2.5 mg/kg (max 200 mg/day) |
| 4. FFP (fresh frozen plasma) i.v., 10 ml/kg – can be used in the absence of the above mentioned drugs \textsuperscript{g} | 3. Antifibrinolytics – when pdC1-INH is not available: | |
| \textsuperscript{g} | – Tranexamic acid (TA) p.o. 20–50 mg/kg/day split into 2 or 3 doses (maximum 3–6 g/day) | – Aminocaproic acid (used less often) |
| 5. Icatibant (Firazyr), s.c., is undergoing clinical studies | \textsuperscript{h} | |

\textsuperscript{a}pdC1-INH \textsubscript{Be}, registered in Europe and the USA for all age groups, for use in home therapy. \textsuperscript{b}pdC1-INH \textsubscript{Be}, registered in Europe from the age of 12 to treat acute attacks and prophylaxis (in the USA registered only for use in long-term prophylaxis). \textsuperscript{c}rhC1-INH registered in Europe and the USA for the treatment of acute attacks from the age of 13 and contraindicated in patients with known or suspected allergy to a rabbit or products of rabbit origin. \textsuperscript{d}Unregistered in Europe, registered in the USA for the treatment of acute attacks from the age of 12; due to the risk of anaphylaxis, this drug should be administered only by a healthcare professional who has medical knowledge on the management of anaphylaxis. \textsuperscript{e}Due to the risk of transfusion transmitted diseases, solvent detergent plasma is preferred over fresh frozen plasma for safety reduction. \textsuperscript{f}Due to the risk of transfusion transmitted diseases, solvent detergent plasma is preferred over fresh frozen plasma for safety reduction. \textsuperscript{g}Dosage for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{h}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{i}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{j}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{k}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{l}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{m}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{n}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{o}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{p}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{q}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{r}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{s}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{t}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{u}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{v}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{w}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{x}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure. \textsuperscript{y}Dosing for short-term prophylaxis has not been established, most experts recommend a dose of 20 U/kg. \textsuperscript{z}Danazol is registered for STP in Europe in children from the age of 12, but not in the USA; it is worth remembering that danazol should be used for not more than 5–7 days before and 2 days after the procedure.

Data on the sex distribution of HAE are varied [12, 13]. Some studies indicate that female sex as well as early onset may result in a more severe course [10]. The symptoms typically become more severe during puberty, especially in women. This was also observed in the presented patients. In the first girl, the symptoms of the disease were recurrent, namely painless swelling of the lips, hands and feet, i.e. typical first HAE symptoms in children [10]. The swelling is often painful, but without pruritus or urticaria. As in the presented cases, it develops within a few hours and usually recedes within a few hours to...
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Conflict of interest
The authors declare no conflict of interest.

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