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HEREDITARY ANGIOEDEMA WITH C1-INH DEFICIENCY IN A UKRAINIAN FAMILY (CASE REPORT)

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Abstract The article presents a family case of HAE with serine endopeptidase C1 inhibitor deficiency in a mother and son. Hereditary angioedema (HAE) is a hereditary disease caused by a defect in the SERPING1 gene (Serpin Peptidase Inhibitor, Clade G (C1 Inhibitor). Changes in this gene lead to pathological functionality or deficiency in the synthesis of the of the protein C1 esterase inhibitor. The function of the C1 Inhibitor protein is to create a proteolytic inactive stoichiometric complex with C1r or C1s proteases, which activates complement, blood coagulation, fibrinolysis, and kinin production. The disease is manifested by the rapid formation of swellings in various places of the body. According to Mansour Ali and colleagues, among pediatric patients, over 50% of cases manifest before the age of 10, and biochemical diagnosis is advisable from the age of 1 year. In the family history, 37-year-old woman has a syndrome of abdominal ischemia with attacks of acute pain syndrome, attacks of angioedema with repeated urgent parenteral applications of antihistamines and corticosteroids. She was referred for an examination to the faculty clinic for recurrent cases of Quincke's edema, where C1INH deficiency was detected in her blood. She confirmed NM_000062.3:p.496_497insGACA; p.Asn166Argfs*92 heterozygous sequence change during molecular genetic research of DNA, by the method of Sanger sequencing in the SERPING1 gene. Mother's family history is complicated: her grandmother died at the age of 50 due to acute respiratory failure due to Quincke's syndrome, mother's sister died at the age of 32 from a similar condition as her mother. During the immunological examination, a C1INH deficiency was detected in the mother, and during molecular genetic research, DNA analysis, using the Sanger sequencing method in the SERPING1 gene, confirmed a heterozygous sequence change. In the 7 year old son examination revealed a low concentration of complement C3 and C4, and extremely low serum concentration of C1INH, other results of serum immunoglobulins IgG, IgA, IgM, C-reactive protein were normal, celiac disease and autoimmune thyropathy were excluded. His genetic examination revealed a heterozygous sequence change in the SERPING1 gene. The variant identified was not previously described in association with HAE at position 257. In addition to the above changes, the subject also had the variant NM_000062.3:c.468CT:p.Ala165 with a population share of less than 1%. Summarizing the results of laboratory examinations and the conclusions of narrow-profile specialists, the patient has a confirmed diagnosis of hereditary angioedema with C1 inhibitor deficiency, according to ICD-10 D841 defect of the complement system. The family was given the drug Berinert for emergency parenteral treatment in case of boy's first attack, the district pediatrician and the doctors of the children's department were informed about the dosage of the drug and the course of treatment. The treatment plan consists of parenteral administration of human C1 inhibitor made from donor plasma at a dose of 20 IU/kg at a rate of 4 ml/min. Conclusions. Early diagnosis of HAE-C1-INH should be performed in all children aged 1 year and older if their parents have recurrent attacks of angioedema. Timely and repeated application of C1 inhibitor concentrate in patients with confirmed NEA-C1-INH allows to prevent severe attacks of laryngeal angioedema and to prevent fatal cases.

Keywords: hereditary angioedema, C1 inhibitor deficiency, C1-INH, serpin peptidase inhibitor, serine/cysteine proteinase inhibitor clade G member 1, family angioedema, pediatric angioedema.

Introduction. Hereditary angioedema (HAE) is a hereditary disease caused by a defect in the SERPING1 gene (Serpin Peptidase Inhibitor, Clade G (C1 Inhibitor). Changes in this gene lead to pathological functionality or deficiency in the synthesis of the of the protein C1 esterase inhibitor.

The aim of the study. Clinical and genetic analysis of two cases of hereditary angioedema in one family.

Object and research methods. Determination of clinical symptoms, blood test results, anamnestic data in mother and son with hereditary angioedema was object research. Methods of study was examination of molecular genetic change of DNA, by the method of Sanger sequencing in the SERPING1 gene.

The function of the C1 Inhibitor protein is to create a proteolytic inactive stoichiometric complex with C1r or C1s proteases, which activates complement, blood coagulation, fibrinolysis, and kinin production [1]. The disease is manifested by the rapid formation of swellings in various places of the body. According to Mansour Ali and colleagues, among pediatric patients, over 50 % of cases manifest before the age of 10, and biochemical diagnosis is advisable from the age of 1 year [2, 3].

Treatment for HAE-C1-INH patients involves the subcutaneous application with C1INH, to prevent repeated attacks of angioedema [4]. In the study of Donald Levy and colleagues, in children undergoing prophylactic treatment, 50 % reduction in the number of attacks was observed compared to the pre-study period [5]. Accordingly, in the examined children, there was 1 attack every 4 weeks, and in 4 children, one attack per year (1 child remained asymptomatic).

Clinical case. From March 2023 7 years old boy is under the supervision of a pediatrician in the Czech

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Republic. He is from Ukraine, moved to the Czech Republic due to the war in Ukraine. His mother, 37 years old woman is observed with the syndrome of abdominal ischemia and repeated attacks of acute pain syndrome in the abdomen, Quincke's edema with repeated urgent parenteral applications of antihistamines and corticosteroids. Boys' maternal grandmother died at the age of 50 due to acute respiratory failure caused by the swelling of the larynx. At the age of 32 mother's sister died of a similar condition as her mother. Boy's father has vitiligo without treatment. A brother from the first marriage of his mother is healthy. Perinatal history is without peculiarities, suspicion of cinnamon food allergy in the form of urticaria is negative. The social anamnesis is satisfactory. The boy attends extra lessons in mathematics and English. The vaccination schedule was disrupted, so in the Czech Republic revaccination with combination vaccines was administrated, as well as tuberculosis vaccination. The post-vaccination course was without complications. Anthropometric values of height and weight correspond to the average percentile data according to his age. Mother was referred for an examination to the faculty clinic for recurrent cases of Quincke's edema, where C1INH deficiency was detected in her blood. She confirmed NM_000062.3:p.496_497insGACA;p.Asn166Argfs*92 heterozygous sequence change during molecular genetic research of DNA, by the method of Sanger sequencing in the SERPING1 gene (Table 1).

Table 1

Results of a molecular genetic examination by Sanger sequencing in mothers SERPING1 gene (genetic laboratory Centrum cardiovascular a transplant surgery, Masaryk University, data provided by Prof. MUDr. Tomash Freiberger, Ph.Dr., Mgr. Viktor Bily)

	Reference sequence	Variant cDNA	Protein	State
GENE SERPING1	NM_000062.3	c.496_497insGACA	p.Asn166Argfs*92	Heterozygous
	NM_000062.3	c.468C>T	p.Ala165=	Heterozygous
	NM_000062.3	c.1029+260G>A	Not confirmed	Heterozygous

Laboratory blood examination of boy detected a low concentration of complement C3 - 0.79 g/l and C4 - 0.07 g/l, extremely low C1INH - 0.081 g/l, other results of serum immunoglobulins IgG, IgA, IgM, C-reactive protein were normal, celiac disease and autoimmune thyropathy were not confirmed.

Genetic examination confirmed the heterozygous sequence change NM_000062.3:c.496_497insGACA; p.Asn166Argfs*92 in the SERPING1 gene in boys' material. From the genetic conclusion in the proband mother's son, there is an insertion of 4 nucleotides in exon 3, which leads to a frame shift in the region of the 166th amino acid position of the C1 inhibitor gene and the formation of a stop codon. This probably leads to degradation of mRNA or premature termination of C1 inhibitor synthesis with subsequent formation of a truncated protein. The variant identified was not previously described in association with HAE at position 257. In addition to the above changes, the subject also had the variant NM_000062.3:c.468CT: p.Ala165 with a population share of less than 1%. Patients gave their consent to the examination and were informed of the results of the genetic study.

Summarizing the results of laboratory examinations and the conclusions of narrow-profile specialists, the patient has a confirmed diagnosis of hereditary angioedema with C1 inhibitor deficiency, according to ICD-10 D841 defect of the complement system. The family was given the drug Berinert for emergency parenteral treatment in case of boys first attack, the district pediatrician and the doctors of the children's department were informed about the dosage of the drug and the course of treatment. Mother currently receives regular scheduled applications of the drug 2 times a month in order to prevent HAE attacks.

Research results and their discussion. Clinical signs of HAE may include, as in the case of mother, attacks of abdominal pain, similar to symptoms of acute abdominal pathology, ischemic abdominal pain, or attacks of obstruction of the upper respiratory tract, similar to Quincke's edema. Frequent manifestations are swelling of the skin of the face, lips, swelling in the genital area, limbs, which are preceded by subjective sensations of paresthesia, pain and impaired functionality of the limb, which were not present in our case. The riskiest attacks of HAE-INH-C1 are swellings in the larynx with manifestations of airway obstruction and acute asphyxia, which leads to acute asphyxia and potential lethality. In the book by Sobotkova and her colleagues in undiagnosed cases of HAE-C1-INH, the mortality is 31.4 %, in contrast to 1.33 % in patients with an established diagnosis [5].

The diagnosis of the disease is based on the determination of the concentration of serum C1-esterase inhibitor, the level of which is about 0.25 g/l, as well as the values of complement C4 and C3, and the exclusion of allergic and non-allergic edema by testing: IgE, ECP.EMA, ATRG, IgA, IgG, IgM [6, 7]

Treatment of the patient involves regular dispensary supervision by a pediatrician, and in the case of acute edematous syndrome, the application of the human C1 inhibitor drug by an emergency physician. An important feature of the disease is the lack of effect from the application of drugs of the antihistamine and corticosteroid groups. The treatment plan consists of parenteral administration of human C1 inhibitor made from donor plasma at a dose of 20 IU/kg at a rate of 4 ml/min, when there is no drug, we give intravenous infusion therapy of donor blood plasma at a dose of 10 ml/kg [7-9]. It is available in Europe Icatibant acetate 30 mg dosage from 10 mg to 30 mg according to the weight of the patient, Conestatum alfa for children dosage 50U/kg, human c1-esterase inhibitor in dosage 500IU, 2000 IU a 3000 IU according to the age of the child, kallikrein inhibitor and antagonist bradykinin receptors – Icatibant acetate [9], during the same time, treatment has evolved from intravenous to subcutaneous and the future will be a focus on oral therapy [10].

Conclusion. Early diagnosis of HAE-C1-INH should be performed in all children from 1 year of age and older if their parents have recurrent attacks of angioedema. Timely and repeated application of C1 inhibitor

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concentrate in patients with confirmed NEA-C1-INH allows to prevent severe attacks of laryngeal angioedema and to prevent fatal cases.

Conflict of interest: absent.

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КЛІНІЧНИЙ ВИПАДОК СПАДКОВОГО АНГІОНЕВРОТИЧНОГО НАБРЯКУ З ДЕФІЦИТОМ БІЛКА С-1 INH В УКРАЇНСЬКІЙ РОДИНІ (КЛІНІЧНИЙ ВИПАДОК)

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Резюме. У статті представлено два сімейні випадки спадкового ангіоедему з дефіцитом інгібітора серинової ендопептидази С1 у матері та сина. У сімейному анамнезі 37-річна пацієнтка, мама 7-річного сина, має синдром абдомінальної ішемії з нападами гострого абдомінального больового синдрому та прояви ангіоневротичного набряку з необхідністю купірування парентеральними антигістамінними та кортикоїдними препаратами. Сімейний анамнез матері ускладнений: бабуся померла у віці 50 років унаслідок гострої дихальної недостатності на тлі синдрому Квінке, сестра матері померла у віці 32 років від такого ж стану. Під час обстеження у матері виявлено дефіцит C1INH, а під час молекулярно-генетичного обстеження підтверджено зміну в гені SERPING1. У сина вказаної пацієнтки виявлено низьку концентрацію комплементу С3 і С4, надзвичайно низьку концентрацію C1INH у сироватці крові. Після проведеного генетичного дослідження у хлопчика виявлено вбудовування 4 нуклеотидів і 3 екзон, що призводить до зсуву рамки в області 166-ї амінокислотної позиції гена інгібітора С1 і утворення стоп-кодону. Це, ймовірно, призводить до деградації мРНК або до передчасного припинення синтезу інгібітора С1 з подальшим утворенням вкороченої структури білка. Варіант, який виявлений, не був описаний у той час у зв'язку зі спадковим ангіоневротичним набряком (HAE) у позиції 257. Окрім вище вказаних змін у хворого виявлено також варіант NM_000062.3:c.468CT:p.Ala165 із популяційною часткою менше 1 %. Пацієнти надали згоду на проведення обстеження та ознайомлені із результатами дослідження. Підсумовуючи вище отримані результати лабораторних обстежень та висновків вузькопрофільних спеціалістів, пацієнт має підтверджений діагноз спадкового ангіоневротичного набряку з дефіцитом інгібітора С1, згідно МКХ-10 код D841 дефект системи комплементу. Генетичне обстеження хлопчина підтвердило гетерозиготну зміну послідовності гена SERPING1. Рання діагностика HAE-C1-INH повинна проводитися в усіх дітей віком від 1 року, якщо у батьків повторюються напади ангіоневротичного набряку. Своєчасне та повторне застосування концентрату інгібітора С1 у пацієнтів із підтвердженим HEA-C1-INH дозволяє запобігти важким нападам ангіоневротичного набряку гортані та попередити летальні випадки.

Ключові слова: сімейний ангіоневротичний набряк, гередитарна ангіоедема, дефіцит білка С1 інгібітора, C1-INH, інгібітор серпін пептидази, інгібітор серин/цистеїнової протеази, агніоневротичний набряк у педіатрії.

Конфлікт інтересів: відсутній.

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