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Review

HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY IN PEDIATRIC PATIENTS IN CROATIA – FIRST NATIONAL STUDY, DIAGNOSTIC AND PROPHYLACTIC CHALLENGES

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SUMMARY – Hereditary angioedema (HAE) is a rare autosomal dominant disease with deficiency (type I) or dysfunction (type II) of C1 inhibitor, caused by mutations in the C1-INH gene, characterized by recurrent submucosal or subcutaneous edemas including skin swelling, abdominal pain and life-threatening episodes of upper airway obstruction. The aim of this study was to investigate healthcare experiences in children with HAE due to C1 inhibitor deficiency (C1-INH-HAE) in Croatia in order to estimate the number of affected children and to recommend management protocols for diagnosis, short-term prophylaxis and acute treatment. Patients were recruited during a 4-year period at five hospitals in Croatia. Complement testing was performed in patients with a positive family history. This pilot study revealed nine pediatric patients positive for C1-INH- HAE type I, aged 1-16 years, four of them asymptomatic. Before the age of one year, C1-INH levels may be lower than in adults; it is advisable to confirm C1-INH-HAE after the age of one year. Plasma-derived C1-INH is recommended as acute and short-term prophylactic treatment. Recombinant C1-INH and icatibant are licensed for the acute treatment of pediatric patients. In Croatia, HAE is still underdiagnosed in pediatric population.

Key words: *Hereditary angioedema types I and II – diagnosis; Complement C1 inhibitor protein; Child; Croatia*

Introduction

Hereditary angioedema (HAE) due to C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disease with deficiency (type I C1-INH--HAE) or dysfunction (type II C1-INH-HAE) of C1 inhibitor (C1-INH) due to mutations in the *SERPING1* gene[1-3]. In some patients with a normal level of C1-INH, angioedema is related to mutation in coagulation factor XII gene (HAE-FXII), plasminogen (HAE-PLG) and angiopoetin-1 (HAE--ANGPT1), or the cause of angioedema remains

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unknown (U-HAE)[2,4]. All types of the disease share the same clinical presentation due to unregulated generation of bradykinin causing leakage of plasma from postcapillary venules[5-7]. Clinical events in the population with C1-INH-HAE are characterized by recurrent submucosal or subcutaneous edemas including skin swelling, abdominal pain and life-threatening episodes of upper airway obstruction. Attacks may occur at any age after birth but early onset of symptoms may predict a more severe course of the disease, which worsens in puberty[8]. The most common attack triggers include mechanical trauma, stress and infections[9,10]. Also, dental-oral procedures, endoscopies or operations in general anesthesia with intubation can precipitate angioedema. If not treated, edema may persist for 1 to 5 days before resolving spontaneously[11]. The earliest and the most common swelling site in pediatric population is subcutaneous edema of the extremities. Upper airway edema is more severe in small children causing death by asphyxiation[12,13]. Abdominal pain, vomiting and diarrhea, frequent in general pediatric population, are present in 80%-90% of HAE patients[8]. Edema can also affect genitalia, urinary bladder, muscles, joints, or can cause migraine or visual disturbances and headache[8]. The aim of this study was to investigate health care experiences in children with HAE in Croatia in order to estimate the number of affected children and to recommend management protocols for establishing HAE diagnosis, short- term prophylaxis before triggering procedures, and acute treatment of pediatric patients.

Patients and Methods

Patients

The patients were recruited during a 4-year period (2012-2016) at five hospitals in Zagreb, Šibenik and Split, Croatia. The diagnosis of C1-INH-HAE was established based on complement testing (complement C4 and C1 inhibitor antigenic levels) and characteristic clinical features such as upper airway and subcutaneous swelling or abdominal pain[14]. It was performed in nine patients from 18 families with confirmed C1-INH-HAE type I diagnosis. A questionnaire (Appendix), developed in line with the international consensus algorithm, was sent to each center, in order to explore patient experiences of the disease, including diagnosis and treatment[2].

The study was approved by the participating hospital ethics committees and a parental written consent was granted.

Complement testing

Serum protein concentrations of C1 inhibitor (normal range: 0.20-0.35 g/L) and C4 (normal range: 0.16-0.31 g/L) were quantified using radial immunodiffusion (Siemens, Marburg, Germany). C1 inhibitor function was measured using an enzyme immunoassay (Quidel Corporation, California, USA) considering C1 inhibitor functional levels ≤40% of normal value as decreased levels. All measurements were performed in accordance with the manufacturer's instructions.

Statistical analysis

No formal statistical hypothesis was tested. Statistical analysis was essentially descriptive (percentages).

Results

Our pilot study identified nine children with HAE with positive family history, aged 0-16 years. All of them tested positive for C1-INH-HAE type I; four of them were asymptomatic (patient 1, age 8; patient 3 age 15; patient 6, age 6; and patient 9, age 1) (Table 1). Detailed clinical data and complement measurements are outlined in Table 1. There were six female (F) and three male (M) patients. Age at onset of symptoms ranged from 1 to 15 years. The prime localization of the attacks was peripheral edema in 55% (5 patients = 3 F, ages 6, 8 and 16; and 2 M, ages 4 and 10), followed by facial swelling in 33% (3 patients = 2 F, ages 16 and 6; and 1 M, age 16), and laryngeal (1 M, age 16) and abdominal edema (1 F, age 6) in one patient (12%) each. Abdominal pain as a symptom of HAE was the prime localization of attacks in patient 8. In patient 2 with facial and neck edema, dental procedures precipitated facial and laryngeal attacks. Presentation of C1-INH-HAE in the upper airways was detected in patient 4. This study identified three adolescents.

Plasma-derived C1-INH (pdC1-INH, human) was administered as acute treatment in the patient with laryngeal, facial and neck edema (20 IU *per* kg body weight by intravenous injection).

In this study, C1-INH-HAE was diagnosed before or immediately after symptom onset.

Table 1. Patient clinical and laboratory data

Patient No.	Gender (M/F)	Age	Age at onset of symptoms	Skin edema	Facial edema	Abdominal edema	Laryngeal edema	Family history	C4 (g/L) (normal range 0.16-0.31)	C1-INH (g/L) (normal range 0.20-0.35)	C1-INH function, %, (decreased ≤40%)
1	F	8	Asympt					+	0.05	0.05	36
2	F	16	15	+	+	-	-	+	0.05	<0.05	30
3	F	15	Asympt					+	0.05	0.05	17
4	M	16	6	+	+	-	+	+	0.06	0.05	20
5	F	8	3	+	-	-	-	+	0.15	0.09	33
6	M	6	Asympt					+	<0.05	0.06	24
7	M	4	1	+	-	-	-	+	0.11	0.13	56
8	F	6	3	+	+	+	-	+	0.07	0.05	33
9	F	1	Asympt					+	<0.05	0.15	48

Asympt = asymptomatic; M = male; F = female; C1-INH = C1 inhibitor

Discussion

Using an estimated prevalence of 1:50 000 and national census statistics of 896 605 children aged 19 years or less in Croatia, approximately 18 children would be expected to have this disease[15]. In this study, we detected nine children with C1-INH-HAE type I from 18 families with positive family history; one of them (patient 4) was the first family member with established proper C1-INH-HAE diagnosis. HAE is a life-altering and chronic disease. This investigation emphasized the variety of clinical presentation of the disease and possible delay in reaching an accurate diagnosis due to that variety. C1-INH-HAE type I diagnosis is corroborated with low levels of serum protein concentrations of C1-INH and C4, and type II with low level of C4 and normal or above normal level of ineffective C1-INH. The diagnosis can be further supported by genetic testing. All neonates/infants with an affected C1-INH-HAE family member should be screened for C1-INH deficiency; genetic testing is indicated under the age of one year[14]. Genetic testing is also indicated for HAE-FXII, HAE-PLG and HAE-ANGPT1 while U-HAE diagnosis can be established with positive family history and typical clinical presentation.

Complement testing is available in clinical centres throughout Croatia, while genetic testing can be performed in collaboration with the University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia, in agreement with the Croatian Health Insurance Fund[10].

Abdominal pain commonly occurs in the general pediatric population. Differential diagnosis can be difficult as abdominal pain is common in pediatric C1-INH-HAE population, as recorded in patient 8[14]. HAE is often underdiagnosed or misdiagnosed as a cause of abdominal pain. During abdominal edema attack, HAE patients are usually observed as cases of gastroenterocolitis or acute abdomen, or may undergo unnecessary surgical procedures[16]. Ultrasound findings of abdominal fluid and bowel swelling can help differentiate patients with HAE[17]. C1-INH-HAE diagnosis should be early established and also considered in patients experiencing recurrent angioedema with poor response to epinephrine, glucocorticoids and antihistamines, since they are ineffective in C1-INH-HAE[1,18-20]. Some children may develop prodromal nonpruritic rash, erythema marginatum, but urticaria with itching at any age practically excludes HAE diagnosis[8,20].

Puberty and oral hormonal contraceptives

Puberty can aggravate the symptoms of HAE, particularly in females, triggered by menstruation and ovulation[9]. Estrogen-containing medications for acne

or oral contraceptives can precipitate attacks, so they are not recommended in patients with HAE[14].

Medical procedures and HAE

Physicians can trigger an HAE attack with their procedures. Dental procedures can precipitate facial and laryngeal attacks, as it was the case in patient 2 with facial and neck edema[13]. Presentation of C1-INH-HAE in the upper airways, as in patient 4, may lead to asphyxiation, the time from symptom onset to asphyxiation varying from as little as 20 minutes to as long as 30 hours, making tracheotomy a lifesaving treatment[13,21]. Education of patients, parents and child care workers about laryngeal symptoms that may lead to asphyxiation, such as hoarseness, lump in the throat or shortness of breath, is crucial. Endoscopy procedures or operations in general anesthesia with intubation that are common in pediatric population, such as adenotonsillectomy or appendectomy, might lead to laryngeal edema or painful abdominal edema. PdC1-INH is recommended as a short-term prophylactic treatment 1-2 hours before triggering procedures at a dose of 20 IU *per* kg body weight by intravenous injection[14]. If pdC1-INH is not available, attenuated oral androgen danazol 5 mg/kg/day or 10 mL/kg solvent detergent plasma (SDP) can be administered[14]. Prophylaxis with danazol should start 5 days before and be continued for 2 days postprocedure. Treatment with pdC1-INH and recombinant C1-INH (rhC1-INH) to replace the functionally or quantitatively deficient C1-INH in patients with HAE has been shown to be effective for treating acute edematous attacks at any site in children. PdC1-INH is licensed for children at any age in a dose of 20 IU *per* kg body weight and rhC1-INH (conestat alfa) or kallikrein inhibitor (ecallantide, only in the USA) for those older than 12 years[14,22]. Conestat alfa should be administrered at a dose of 50 IU *per* kg body weight by intravenous injection[15]. Icatibant administered in children and adolescents subcutaneously based on body weight has been recently approved for children above the age of 2 years[15]. Icatibant is approved for self-administration, allowing patients/families to take control of their disease. SDP is indicated in emergency situations when licensed therapy is not available (or fresh frozen plasma (FFP) as a source of C1-INH). Individuals with HAE require lifelong therapy and evaluation of disease activity.

In conclusion, HAE is still underdiagnosed in pediatric population. This was the first survey of pediatric HAE in Croatia. According to these findings, we recommend comprehensive care, not only parental or medical, but also of all those included in the process of education in schools or kindergartens[23]. Also, identification card with individual treatment plan made by HAE specialist must be provided for each pediatric HAE patient. Dental-oral procedures, endoscopies or operations in general anesthesia can precipitate angioedema. Plasma-derived C1-INH is recommended as short-term prophylactic treatment before triggering procedures. Plasma-derived C1-INH, recombinant C1-INH (for children above 12 years) and icatibant (for children above 2 years) are licensed for the acute treatment of pediatric patients. Raising awareness about rare diseases among parents and physicians is essential for early and accurate establishment of the diagnosis, effective management of acute attacks and prior to triggering procedures in order to avoid unnecessary investigations and to prevent adverse events.

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Appendix
Questionnaire for patients with hereditary angioedema

UPITNIK ZA PACIJENTE S HEREDITARNIM ANGIOEDEMOM

Datum _____ datum rođenja _____

Ime i prezime _____

MOLIM PODVUĆI:

– dob pojave bolesti:
0-5 godina; 6-10 godina; 11-20 godina; >20 godina

– imao/la sam:
edem kože, bolni edem trbuha, edem grkljana, druge kliničke manifestacije

Znakovi bolesti **posljednjih mjesec dana (navesti)**:

_____

Uzimate li profilaksu (npr. Danazol tbl) DA NE

Ako DA navedite koju _____

označiti križićem:

Znakovi bolesti	Nema smetnji	Malo uznemirujuće	Neugodne smetnje	Jako uznemirujuće	Išao sam na hitni prijam	Koliko su česte u godini dana? Prije preventivne th/ nakon preventivne th
Otekline po koži udova, trupa						
Otekline lica						
Otekline grla						
Bolovi u trbuhu						

Znakovi bolesti **prije započimanja preventivne terapije**
(molim navesti znakove bolesti i koliko puta godišnje su se javile):

_____

Što Vam izaziva napade bolesti? Molim podvući
infekcija napor trauma hormonska kontracepcija
Ostalo, što _____

Jeste li alergični na neki lijek? DA NE
Ako DA koji? _____

Bolujete li od neke druge bolesti? DA NE
ako Da koje _____

Uzimate li lijekove (navesti koje)? _____

Imate li kod sebe lijek Berinert za samopomoć? DA NE
Imate li kod sebe lijek Firazyr za samopomoć? DA NE
Jeste li ikada primijenili lijek za samopomoć? DA NE
Jeste li ikada dobili neki od navedenih lijekova na hitnom prijmu? DA NE

Jeste li ikada imali ikakvu intervenciju (intubacija, traheotomija)? DA NE
Ako DA koju intervenciju? _____

Koju terapiju dobijete u akutnoj epizodi? _____
_____

Vaši nalazi:
Koncentracija C4 _____ Koncentracija C1 inhibitora _____

Imate li stečeno pomanjkanje C1 inhibitora? DA NE

Bolesni srodnici (npr. otac, sin…): _____
_____

Klinički zdravi srodnici (nemaju simptome bolesti) s laboratorijski potvrđenim manjkom C1 inh (i sniženim C4)
_____
_____

Srodnici koje možemo pozvati na testiranje: _____
_____

Obiteljsko stablo:

Suglasan sam s provođenjem genetske analize gena za hereditarni angioedem.

Ime i prezime _____ datum _____

ništa jako
Koliko Vas bolest ometa u svakodnevnom životu? 1 2 3 4 5
Koliko Vas bolest ometa na poslu? 1 2 3 4 5
Jeste li kada doživjeli neugodnosti radi bolesti? 1 2 3 4 5
Smeta li Vašem partneru Vaša bolest? 1 2 3 4 5
Utječe li Vaša bolest na kvalitetu Vašeg života? 1 2 3 4 5
Utječe li Vaša bolest na kvalitetu života Vaše obitelji? 1 2 3 4 5
Jeste li član neke od udruga oboljelih od HAE? DA NE

Kako se informirate o svojoj bolesti? _____
_____

Što biste predložili kao mjeru unaprjeđenja zdravstvene skrbi ili kvalitete života za oboljele od HAE?
_____
_____

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Sažetak

HEREDITARNI ANGIOEDEM UZROKOVAN MANJKOM C1-INHIBITORA U PEDIJATRIJSKIH BOLESNIKA U HRVATSKOJ – PRVO NACIONALNO ISTRAŽIVANJE, DIJAGNOSTIČKI I PROFILAKTIČKI IZAZOVI

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Hereditarni angioedem (HAE) je rijetka autosomno dominantna bolest nastala zbog mutacije gena *SERPING1* za inhibitor plazmatskog proteina C1 (C1-INH). Uslijed manjka C1 inhibitora (tip I) ili njegove disfunkcionalnosti (tip II) dolazi do okidačem potaknute autoaktivacije C1-komponente komplementa i cijele kaskade koja dovodi do submukoznih ili subkutanih iznenadnih pojava oteklina kože, lica, kapaka, usana ili grla te abdominalnih bolova praćenih povraćanjem i dehidracijom. U najtežim slučajevima uslijed edema glotisa može doći do gušenja. Cilj ovoga istraživanja bila je procjena ukupnog broja djece s HAE zbog nedostatka C1 inhibitora (C1-INH-HAE) u Hrvatskoj kako bi se preporučili i provodili ujednačeni protokoli za dijagnozu, kratkotrajnu profilaksu i akutno liječenje. Pedijatrijski bolesnici su uključivani u istraživanje tijekom 4 godine u pet bolnica u Hrvatskoj. Svima s pozitivnom obiteljskom anamnezom na HAE analizirana je razina komplementa i C1 inhibitora. Probno istraživanje je otkrilo devet bolesnika pedijatrijske populacije u dobi od 1-16 godina koji su pozitivni za CI-INH-HAE tip I, od kojih su 4 bili asimptomatski. U slučaju akutnog napadaja HAE kao i za profilaktičnu primjenu preporuča se primjena pdC1-INH (humani inhibitor C1 esteraze). Također, rekombinantni C1-INH i ikatibant indicirani su za akutno liječenje pedijatrijskih bolesnika. U Hrvatskoj HAE je još uvijek nedovoljno dijagnosticiran u pedijatrijskoj populaciji.

Ključne riječi: *Hereditarni angioedem, tipovi I i II – dijagnostika; Komplement C1 inhibitor protein, Dijete; Hrvatska*