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Acquired Arnold-Chiari malformation in a 16-year-old patient with hereditary angioedema

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To the editor,

A 16-year-old male patient, presented with one month-history of complaints of an acute pain in the neck, accompanied by relapsing acute headache, sometimes irradiating forward the left arm. The patient had been diagnosed with hereditary angioedema (HAE) type I at age of 7, because of recurrent, non-pruritic edemas, affecting the skin of the face, neck, chest and abdomen, accompanied by colic-like intestinal spasms and relapsing bronchospasms, occurring without provocation and laboratory confirmed low serum levels of C1 inhibitor (Fig. 1a,b). The patient had been treated with recombinant C1-esterase inhibitors for 9 years, with satisfactory therapeutic response and decreasing of the attacks, during this period.

The clinical examination revealed slight rigidity in the cervical part of the spine. Conducted laboratory tests, including total and differential blood count, biochemistry, hormonal status and immunology did not show any abnormalities from the normal ranges. Imaging diagnostic procedures observed markedly incarceration of cerebellar tonsils in the foramen magnum and arc of C1, syringomyelic cavity, affecting the level from C3 to C6, extended dimensions of the pituitary gland, resembling pituitary microadenoma within normal levels of pituitary hormones (Fig. 2a,b).

The diagnosis of Arnold-Chiari malformation type I was made based on the imaging findings and clinical symptoms. Syringomyelia was also observed, as a result from the impaired drainage of cerebrospinal fluid. The patient underwent surgical suboccipital decompression with removal of foramen magnum and C1 laminectomy, via craniotomy suboccipitalis. The enlarged tonsils were fenestrated and decreased in size, followed by wide opening of foramen Magendie. Plastic recovery of the dura was performed, by using periost from the occipital area.

First identified in 1883 by Cleland, Arnold Chiari malformation (ACM) is characterized by caudal displacement of the cerebellar tonsils that penetrate into the spinal canal through the foramen magnum (1,2). The condition is a result from structural defects in the brain and spinal cord, leading to impaired cerebrospinal fluid (1). Most cases of Chiari malformations occur during fetal development while much less commonly, they can occur later in life (3).

Scoliosis, kyphosis, hydrocephalus, platybasia, occipitalization, basilar invagination and Syringomyelic cavities could be associated with ACM type 1, as syringomyelia can develop into progressive neurological deterioration (4). It has been postulated that type I is the only type of Chiari malformation that can be acquired, usually as a result from an excessive amount of cerebrospinal fluid is drained away because of injury, infection and chronic exposure to toxic substances in young adults (3,4). In the presented case, the clinical manifestation of the malformation occurred at age of 16, within the framework of hereditary angioedema type 1, treated with recombinant C1 inhibitor for 9 years. Type I is the most common type of HAE, inherited in autosomal-dominant pattern, as a result from an aberration in the gene coding for the plasma protein C1-inhibitor, leading to decreased levels of the inhibitor for the first component of the complement pathway (C1-INH) (5,6). The clinical substrate – non-pruritic edemas, occur due to increased production of bradykinin, formed as insufficient C1 inhibitor activity fails to restrict the action of factor XII and kallikrein (5).

The biologic activities of C1 inhibitor is generally focus on the regulation of vascular permeability and anti-inflammatory functions (7). The control of vascular permeability is exerted through inhibition of two of the proteases involved in the generation of bradykinin, factor XIIa and plasma kallikrein, while the anti-inflammatory functions are exerted mainly via inhibition of complement system proteases and the plasma kallikrein-kinin system proteases (7). Furthermore, concentration of C1 inhibitor at sites of inflammation, inhibition of alternative complement pathway activation, inhibition of the biologic activities of gram negative endotoxin, enhancement of bacterial phagocytosis and killing, and suppression of the influx of leukocytes into a site of inflammation play role as additional function in homeostasis (7,8) . The inhibition of C1 part of the classical complement pathway participates in the regulation of various body functions, including intra and extracellular flow of body fluids (7,8). HAE is clinically characterized by recurrent acute swelling episodes on the extremities, abdomen, face, trunk, or airways, as a result from increased vascular permeability (5,6). The episodes are variable in terms, severity, location and frequency, as they may occur spontaneously or may be triggered by curtain stimuli, including trauma, stress, or infections (6). The associated clinical symptoms include noninflammatory swellings of the skin and mucous membranes, vomiting, diarrhea, paroxysmal colicky pain, laryngeal edema and upper airway obstruction, while erythema marginatum may precede the occurrence of edema in 25% of the cases (5).

We present a case of acquired ACM type 1 in a 16-year-old male patient, with long-lasting hereditary angioedema type 1, treated with recombinant C1 esterase inhibitors for 9 years. To the best of our knowledge, this is the first report in the literature of such association. Although it has been postulated that ACM could be acquired at later ages, as a result of trauma, injury or toxic substance exposure (3), the limited literature data on this issue hinder the hypothesis for eventual pathogenetic relationship between these two rare conditions. In the presented case, the impaired cerebrospinal fluid, resulting in clinical manifestation of ACM at later age, could be provoked from by the chronic increased production of bradykinin, formed as insufficient C1 inhibitor activity in patient with HAE, with further failure of the restriction of the action of factor XII and kallikrein. We couldn't find any literature data, supporting or denying the idea for triggering the acquired malformation by chronic increased vascular permeability or chronic exposure to certain drugs. The presented case of association of ACM in patient with hereditary angioedema remains this question open for further investigations.

References:

1. Speer MC, Enterline DS, Mehlretter L, Hammock P, Joseph J, Dickerson M, Ellenbogen RG, Milhorat TH, Hauser MA, George TM. Chiari Type I Malformation with or Without Syringomyelia: Prevalence and Genetics. *J Genet Couns*. 2003; 12(4):297-311.
2. Moscote-Salazar LR, Calderón-Miranda WG, Alvis-Miranda HR, Lee-Aguirre Á, Alcalá-Cerra G. Type I Chiari malformation associated with cerebellar atrophy. Case report. *Rev Med Inst Mex Seguro Soc*. 2017; 55(2):260-263.
3. Ghaly RF, Tverdohleb T, Candido KD, Knezevic NN. Management of parturients in active labor with Arnold Chiari malformation, tonsillar herniation, and syringomyelia. *Surg Neurol Int*. 2017; 8:10. doi: 10.4103/2152-7806.198737.
4. Meadows J, Kraut M, Guarnieri M, Haroun RI, Carson BS. Asymptomatic Chiari Type I malformations identified on magnetic resonance imaging. *J Neurosurg*. 2000; 92(6):920-6.
5. KE. Binkley. Factor XII mutations, estrogen-dependent inherited angioedema, and related conditions. *Allergy Asthma Clin Immunol*. 2010; 6(1): 16.
6. UC. Steiner, C. Weber-Chrysochoou, A. Helbling, K. Scherer, PS. Grendelmeier, WA. Wuillemin. Hereditary angioedema due to C1 - inhibitor deficiency in Switzerland: clinical characteristics and therapeutic modalities within a cohort study. *Orphanet J Rare Dis*. 2016; 11: 43.

7. AE. Davis, P. Mejia, F. Lu. Biological activities of C1 inhibitor. Mol Immunol. Mol Immunol. 2008; 45(16): 4057–4063.
8. AE. Davis, S. Cai, D. Liu. C1 inhibitor: Biologic activities that are independent of protease inhibition. Immunobiology. 2007; 212(4-5): 313–323.

