



Commentary

Specific IgE levels in pericardial and cerebrospinal fluids in forensic casework



Immunoglobulins E (IgE) constitute an important regulator of allergic reactions as they bind to high and low affinity FcεRI and FcεRII receptors respectively. These antibodies get attached on the eosinophil, platelet, mast, macrophage, monocyte and dendritic cell surface thus contributing to immunological procedures. IgE's targets likely extend beyond these cells to contribute to immunological procedures or to induce coronary events [1] but even to diagnostic purposes in the forensic setting.

In the very interesting paper published in *Forensic Science International* [2], Palmieri et al. measured levels of total and specific IgE in 54 postmortem serum samples from femoral blood, pericardial and cerebrospinal fluid in 3 groups of deaths: non-allergic deaths in non-atopic individuals, fatal allergic anaphylaxis deaths and non-allergic deaths in individuals without medical records. In an effort to evaluate the usefulness of measuring total and specific IgE in pericardial and cerebrospinal fluid for diagnostic purposes in case of blood unavailability, IgE levels were reported to be significantly higher in femoral blood and pericardial fluid than in the cerebrospinal fluid samples. Specific IgE antibodies were revealed only in postmortem serum from femoral blood and pericardial fluid. It was concluded that, total IgE measurements, using a cutoff value of 60 kU/l in femoral blood and 52 kU/l in pericardial fluid, were suggestive of an atopic disposition for the concerned patients. Specific IgE measurements, using a cutoff value of 0.35 kU/l, in both postmortem serum and pericardial fluid, were also suggestive of an atopic disposition. The authors correctly emphasized that increased IgE levels “do not prove that death was preceded by IgE-mediated anaphylaxis but can only suggest antemortem atopic disposition and the degree of specific allergen sensitization in individual cases”.

The principal aim of Palmieri's et al. work was to evaluate the usefulness of IgE determination in pericardial and cerebrospinal fluid so as to diagnose the cause as well as the conditions of such a death. Sudden death accounts for approximately two-thirds of all autopsies in forensic medicine [3]. Cardiac deaths account for 50% of all deaths in developed and 25% in the developing world [4]. On the other hand anaphylaxis via mast cell activation may accompany up to 13% of sudden unexpected deaths in adults [5]. Indeed, the heart is considered as the primary door through which life crosses to death. Since the heart and especially the coronary arteries are regarded as the primary targets of anaphylaxis [6] and the pericardial fluid is considered as plasma ultrafiltrate from both epicardial capillaries and from interstitial fluid within the underlying myocardium, the pericardium could hide the secret and the cause of undiagnosed sudden deaths. In this aspect, searching for molecules, related to anaphylaxis, in the sac

surrounding the heart, as Palmieri et al. have performed from the first time, is a very challenging attempt.

The pericardium (from the Greek περί ‘around’ and καρδία ‘heart’) is a two layer sac containing the heart and the roots of the great vessels. The pericardial fluid is secreted by the visceral pericardium and is concentrated in the space between the parietal and visceral layers. Normally this fluid has a volume of approximately 20–60 ml disposing a lubricating function. It is a plasma ultrafiltrate and many of its molecules are in close affinity to those found in plasma. Several factors, including coronary artery disease, allergic diseases, systemic diseases, malignant diseases, connective tissue disorders, infections, and idiopathic causes can increase the amount and change the pericardial fluid composition [7]. In the realm of forensic pathology, several specific molecules have been measured for diagnostic purposes. These include, among others, markers of myocardial damage (such as cardiac troponins and immunoglobulins) [8,9].

The minimal amount of IgE detection from 4 kU/l to 11 kU/l in the cerebrospinal fluid samples could be explained by the fact that the brain does not suffer from anaphylaxis because IgE does not cross the blood–brain barrier [10]. The blood–cerebrospinal fluid barrier is a mechanism that plays a critical role in the maintenance of normal brain function. This barrier is composed by the choroid plexus, which secretes cerebrospinal fluid and prevents the entrance of substances from the blood into the brain and cerebrospinal fluid. The establishment of distinct fluid compartments within the brain has been attributed to “tight junctions” in the cerebrospinal space function that act as a seal to regulate lateral diffusion between the apical and basolateral plasma membrane [11]. The minimal presence of specific IgE in the cerebrospinal fluid might be due to local production and not to simple transudation through the blood–brain barrier [12]. Indeed, in a study of 7 young patients with cerebral ventricular shunts and allergy to latex caused from repeated intracerebral operations for intraventricular hemorrhage [13], the latex-specific IgE levels in blood and in cerebrospinal fluid were similar, while the total IgE in the cerebrospinal fluid was very low. These results indicate that IgE detected in cerebrospinal fluid has been synthesized locally and is not the consequence of a leaky hemato–encephalic barrier. On the contrary, other investigators believe that IgE in allergic to latex patients from various surgical procedures for ventriculoperitoneal shunt can transudate into the cerebrospinal fluid [14]. It should be emphasized that additional measures for diagnosis and confirmation of an anaphylactic sudden death that should include histological examination of several tissues in the dead human body are necessary. The searching for eosinophils and mast cell infiltration in the spleen combined with serum tryptase measurement that could diagnose anaphylaxis and anaphylactic death with a high degree of certainty has been already proposed [15]. The examination of other tissues infiltrated by allergic inflammatory

cells could be proven of paramount importance in diagnosing anaphylactic sudden death. However, anaphylactic death cannot be diagnosed by autopsy alone or by counting mast cells in the lung and airways because these methods have failed to give consistent results [16]. Coronary artery histology, although laborious, offers great help in elucidating and confirming anaphylactic death. This is based on the followings:

- 1 Patients who had died suddenly from coronary artery spasm attacks had increased number of mast cells in coronary intima, media and adventitia [17].
- 2 Coronary arteries of cardiac patients are hyper-reactive and contain stores of amines deriving from inflammatory cells that are the main culprits in inducing coronary spasm and death [18].
- 3 Histological examination of patients with coronary stent implantation, who had died from stent thrombosis due to Kounis syndrome, has revealed that the coronary tunica adventitia was infiltrated by scattered mast cells [19,20].

As Palmiere et al. have emphasized, fatal anaphylaxis as a cause of death should not be confirmed only by detailed previous personal history, in-depth forensic investigations including measurement of mast cell-derived tryptase, total IgE and specific IgE, but needs also additional immunohistochemical documentation of the presence of activated mast cell and eosinophil tissue infiltration.

References

- [1] N.G. Kounis, G. Hahalis, Serum IgE levels in coronary artery disease, *Atherosclerosis* 251 (2016) 498–500.
- [2] L. Tran, B. Astengo, C. Palmiere, Determination of specific IgE in pericardial and cerebrospinal fluids in forensic casework, *Forensic Sci. Int.* 267 (2016) 204–209.
- [3] R.B. Singh, J.P. Sharma, V. Rastogi, M.A. Niaz, S. Ghosh, R. Beegom, E.D. Janus, Social class and coronary disease in rural population of north India. The Indian social class and heart survey, *Eur. Heart J.* 18 (1997) 588–595.
- [4] S. Pell, W.E. Fayerweather, Trends in the incidence of myocardial infarction and in associated mortality and morbidity in a large employed population 1957–1983, *N. Engl. J. Med.* 312 (1985) 1005–1011.
- [5] H.J. Schwartz, J.W. Yunginger, L.B. Schwartz, Is unrecognized anaphylaxis a cause of sudden unexpected death? *Clin. Exp. Allergy* 25 (1995) 866–870.
- [6] N.G. Kounis, P. Davlouros, G. Hahalis, A. Mazarakis, The heart seems to be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome, *Intern. Emerg. Med.* 7 (Suppl. 2) (2012) S119–120.
- [7] Y. Adler, P. Charron, M. Imazio, L. Badano, G. Barón-Esquivias, J. Bogaert, A. Brucato, P. Gueret, K. Klingel, C. Lionis, B. Maisch, B. Mayosi, A. Pavie, A.D. Ristić, M. Sabaté Tenas, P. Seferovic, K. Swedberg, W. Tomkowski, S. Achenbach, S. Agewall, N. Al-Attar, J. Angel Ferrer, M. Arad, R. Asteggiano, H. Bueno, A.L. Caforio, S. Carerj, C. Ceconi, A. Evangelista, F. Flachskampf, G. Giannakoulas, S. Gielen, G. Habib, P. Kolh, E. Lambrinou, P. Lancellotti, G. Lazaros, A. Linhart, P. Meurin, K. Nieman, M.F. Piepoli, S. Price, J. Roos-Hesselink, F. Roubille, F. Ruschitzka, J. Sagristà Saulea, M. Sousa-Uva, J. Uwe Voigt, J. Luis Zamorano, European Society of Cardiology (ESC), 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European society of cardiology (ESC) endorsed by: the European association for cardio-thoracic surgery (EACTS), *Eur. Heart J.* 36 (2015) 2921–2964.
- [8] P.S. Ghormade, N.B. Kumar, C.V. Tingne, A.N. Keoliya, Distribution and diagnostic efficacy of cardiac markers CK-MB & LDH in pericardial fluid for postmortem diagnosis of ischemic heart disease, *J. Forensic Leg. Med.* 28 (2014) 42–46.
- [9] S. Ben-Horin, A. Shinfeld, E. Kachel, A. Chetrit, A. Livneh, The composition of normal pericardial fluid and its implications for diagnosing pericardial effusions, *Am. J. Med.* 118 (2005) 636–640.
- [10] T.C. Theoharides, Mast cells and stress-a psychoneuroimmunological perspective, *J. Clin. Psychopharmacol.* 22 (2002) 103–108.
- [11] E.E. Schneeberger, R.D. Lynch, The tight junction: a multifunctional complex, *Am. J. Physiol. Cell Physiol.* 286 (2004) C1213–C1228.
- [12] M.E. Rothenberg, Eosinophilia, *N. Engl. J. Med.* 338 (1998) 1592–1600.
- [13] B. Niggemann, A. Bauer, K. Jendroska, U. Wahn, Latex allergy as a cause of eosinophilia in cerebrospinal fluid in a child with a ventricular shunt, *J. Allergy Clin. Immunol.* 100 (1997) 849–950.
- [14] A.B. Sá, M.C. Mallozi, N. Zanon, D. Solé, Latex-specific IgE and its recombinant fractions in a child with cerebrospinal eosinophilia, *Allergol. Immunopathol. (Madr.)* 42 (2014) 504–505.
- [15] E. Edston, Accumulation of eosinophils, mast cells, and basophils in the spleen in anaphylactic deaths, *Forensic Sci. Med. Pathol.* 9 (2013) 496–500.
- [16] C. Palmiere, Postmortem diagnosis of drug-induced anaphylactic death, *J. Forensic Leg. Med.* 41 (2016) 28–29.
- [17] M.B. Forman, J.A. Oates, D. Robertson, R.M. Robertson, L.J. Roberts II, R. Virmani, Increased adventitial mast cells in a patient with coronary spasm, *N. Engl. J. Med.* 313 (1985) 1138–1141.
- [18] S. Kalsner, R. Richards, Coronary arteries of cardiac patients are hyperreactive and contain stores of amines: a mechanism for coronary spasm, *Science* 223 (1984) 1435–1437.
- [19] N.G. Kounis, G.N. Kounis, G.D. Soufras, Kounis syndrome: a potential cause of simultaneous multivessel coronary spasm and thrombosis after drug-eluting stent implantation, *J. Invasive Cardiol.* 19 (2007) 200–201.
- [20] B.C. Brott, A.S. Anayiotos, C.D. Chapman, P.G. Anderson, W.B. Hillegass, Severe, diffuse coronary artery spasm after drug-eluting stent placement, *J. Invasive Cardiol.* 18 (2006) 584–592.

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