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Revue française d'allergologie 62 (2022) 287–288

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Tryptase and anaphylaxis: The case for systematic paired samples in all settings, from the playground to the COVID-19 vaccination center

Tryptase et anaphylaxie : de l'aire de jeux au centre de vaccination COVID, deux prélèvements sont nécessaires en toutes circonstances

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ARTICLE INFO

Article history:
Received 7 February 2022
Accepted 8 February 2022
Available online 11 February 2022

ARTICLE INFO

Keywords:
Anaphylaxis
Hypersensitivity
Mast cell
Tryptase

Mots clés :
Anaphylaxie
Hypersensibilité
Mastocyte
Tryptase

Anaphylaxis is an immediate and potentially life threatening systemic reaction [1], associated with significant morbidity, mortality and much too frequent suboptimal management. Serum tryptase is the main and most widely available mast cell biomarker available for in vitro diagnostics. In the clinical setting, tryptase determination is commonly performed using the "total tryptase assay" (ImmunoCAP Tryptase, Thermo Fisher Scientific, Uppsala, Sweden), which has received significant technical improvement and related changes in median and upper limit values since its first release in 1995 [2]. Taking two tryptase samples with adequate timing has been recommended for the diagnosis of anaphylaxis and may also add mechanistic information. Indeed, anaphylaxis by itself does not provide clues for the underlying mechanism [2].

Adequate timing refers to paired acute (sAT) and baseline (sBT) serum tryptase determination, with sAT sample optimally taken 30-120 min after the onset of signs or symptoms and sBT sample drawn at least 24 hours after the complete resolution of all signs and symptoms. The current international consensus states that a transient elevation of sAT greater than $[2 + (1.2 \times \text{sBT})]$ is indicative of mast cell degranulation [3]. This algorithm allows calculating an individual cut-off for each patient, based on sAT and sBT values: sAT exceeding $[2 + (1.2 \times \text{sBT})]$ µg/L supports mast cell degranulation, even in cases when sAT remains in the normal reference range.

Paired sAT and sBT determination increases both the sensitivity and the specificity of anaphylaxis diagnosis [2], assists with severity grading [4] and since recently help identify patients at increased risk of severe reactions due to the hereditary alpha-tryptasemia genetic trait [5]. In fact, proper interpretation of both sAT and sBT can only be done using paired samples. For example, recent data on hereditary alpha tryptasemia have provided further support for systematic testing of paired sAT and sBT. With a prevalence of up to 8% in general population and most studies showing an increased risk of severe hypersensitivity reactions, no clinician should take the risk of overlooking hereditary alpha-tryptasemia, which can only be suspected through sBT determination and confirmed with

Abbreviations: sAT, serum acute tryptase; sBT, serum baseline tryptase.

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https://doi.org/10.1016/j.reval.2022.02.218

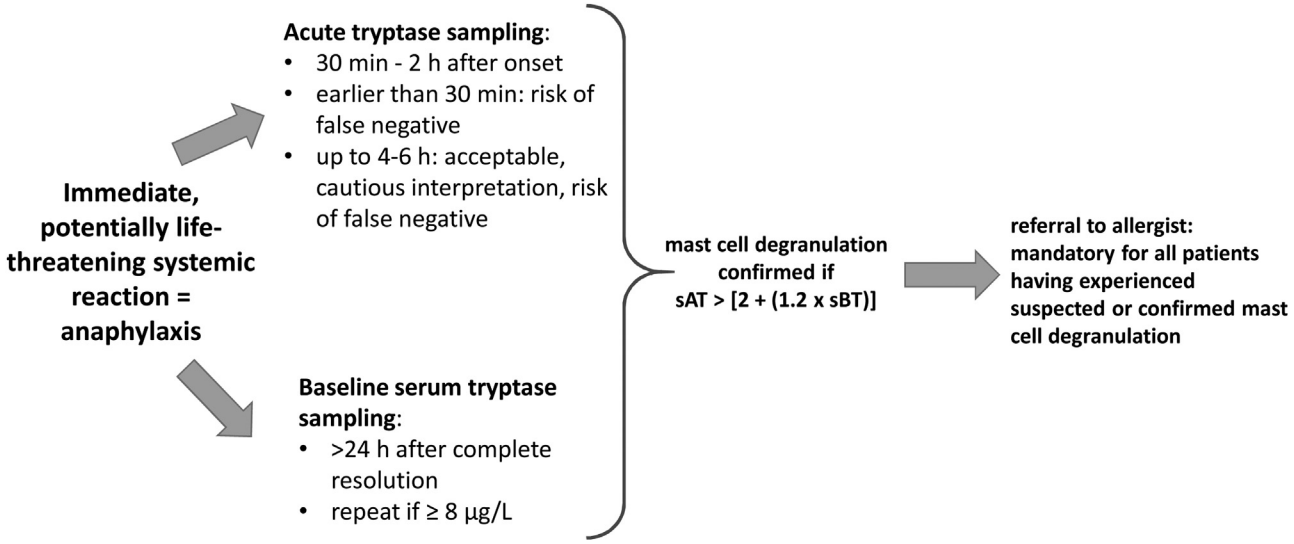

Fig. 1. Paired tryptase sampling in anaphylaxis.

digital droplet PCR in specialized laboratories. Missing other mast cell-related disorders, such as mastocytosis, often discovered as an elevated sBT, may lead to substandard patient management, which would have been avoidable through proper tryptase assessment.

Among other frequent errors, we would like to cite the assumption that the manufacturer's upper limit for serum tryptase (currently 11.0 µg/L in Europe) is a reliable cut-off for discriminating mast cell degranulation. This assumption has been abundantly demonstrated as false by large cohort studies on perioperative anaphylaxis, showing that up to 60% of confirmed mast cell degranulation events had sAT lower than the manufacturer's cut-off [2,6].

In some patients, especially in those with extremely high sAT, serum tryptase levels may not return to baseline after 24 h; therefore, if a sample taken after 24 h is higher than 8 µg/L or even 7 µg/L, a control sBT sample should be taken later, for example during the allergy work-up which must be offered to any patient having experienced anaphylaxis.

Further support for the paired sAT and sBT determination comes from its robust use in populations such as children [7] and pregnant women [8].

To summarize, taking two tryptase samples at adequate times for acute and baseline serum tryptase assessment and interpretation is the current state of the art recommendation for anaphylaxis (Fig. 1). This recommendation should be kept in mind and implemented in any case of anaphylaxis or suspicion of immediate hypersensitivity reaction, should it happen at home, at school, in the office, during an anesthetic procedure, while delivering a COVID-19 vaccine, or in any other setting. Proper sampling time is critical for acute tryptase measurement, and baseline sampling must not be overlooked.

Disclosure of interest

JV reports speaker and consultancy fees in the past 5 years from Meda Pharma (Mylan), Novartis, Sanofi, Thermo Fisher Scientific, outside the submitted work.

The other authors declare that they have no competing interests in relation to this study.

References

[1] de Silva D, Singh C, Muraro A, Worm M, Alviani C, Cardona V, et al. Diagnosing, managing and preventing anaphylaxis: systematic review. Allergy 2021;76(5):1493–506.
[2] Vitte J, Sabato V, Tacquard C, Garvey LH, Michel M, Mertes PM, et al. Use and interpretation of acute and baseline tryptase in perioperative hypersensitivity and anaphylaxis. J Allergy Clin Immunol Pract 2021;9(8):2994–3005.
[3] Valent P, Bonadonna P, Hartmann K, Broesby-Olsen S, Brockow K, Butterfield JH, et al. Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe systemic mast cell activation and mast cell activation syndrome. Int Arch Allergy Immunol 2019;180(1):44–51.
[4] Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. Allergy 2019;74(10):1872–84.
[5] Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Selb J, Zanotti R, et al. Heritable risk for severe anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. J Allergy Clin Immunol 2021;147(2):622–32.
[6] Egner W, Sargur R, Shrimpton A, York M, Green K. A 17-year experience in perioperative anaphylaxis 1998–2015: harmonizing optimal detection of mast cell mediator release. Clin Exp Allergy 2016;46(11):1465–73.
[7] De Schryver S, Halbrich M, Clarke A, La Vieille S, Eisman H, Alizadehfar R, et al. Tryptase levels in children presenting with anaphylaxis: temporal trends and associated factors. J Allergy Clin Immunol 2016;137(4):1138–42.
[8] McCall SJ, Bonnet MP, Ayras O, Vandenberghe G, Gissler M, Zhang WH, et al. Anaphylaxis in pregnancy: a population-based multinational European study. Anaesthesia 2020;75(11):1469–75.