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Idiopathic anaphylaxis

SHORT CASE REPORT

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An acute increase in tryptase levels is a reliable indicator of mast cell activation. Here, we present a case in which acute measurement of tryptase revealed a rare and potentially serious condition. The report is a reminder of how a correct diagnosis can depend on performing the right test at the right time.

A woman in her forties was referred to the allergology outpatient clinic after repeated episodes of tachycardia, flushing and near syncope, each lasting approximately ten minutes. The episodes were accompanied by nasal congestion and rhinorrhoea, and sometimes by palmar itching, shortness of breath, abdominal pain and urinary urgency. After each episode, she would develop a headache and pronounced fatigue. The

episodes had begun five years earlier, with the first episode awakening the patient from sleep. She had subsequently experienced repeated episodes at irregular intervals with no discernible trigger.

After the first episode, the patient was referred by her general practitioner (GP) to the medical department to be investigated for possible carcinoid syndrome, but an endocrinologist ruled out a neuroendocrine tumour. A month later, she had another attack and was admitted to the acute medical unit, and from there she was referred to a neurologist on suspicion of possible epilepsy. Cardiac function was also assessed during the admission. Echocardiography was normal, but Holter monitoring revealed runs of supraventricular tachycardia and a rapid pulse prior to syncope. This was interpreted as a vasovagal response with compensatory tachycardia, and metoprolol tablets were used to manage the supraventricular tachycardias. Two months later, a neurologist ruled out epilepsy on the basis of a sleep-deprived electroencephalogram. Head MRI with intravenous contrast and cerebral angiography were also normal.

Six months later, the attacks were still occurring, and the patient's GP therefore referred her back to the medical department, even though her previous assessment had not led to a diagnosis. A new round of testing revealed Graves' disease. Because of the continuing attacks, as well as persistently elevated tryptase levels at 17 mcg/L, the patient underwent a bone marrow biopsy to assess the possibility of mastocytosis, but the results were negative. Graves' disease can cause flushing and a rapid heartbeat, but the patient's episodes continued even after normalisation of her thyroid hormone levels with carbimazole, although she did have fewer episodes for a while.

Two years later, the attacks increased in frequency again, and the GP referred the patient to a private otorhinolaryngologist to be assessed for possible allergies. Blood samples were taken on suspicion of allergies or angioedema. These showed total IgE 32 kU/L (reference range < 120), tryptase 16.5 mcg/L (< 12), C3 1.0 g/L (0.83–1.65), C4 0.16 g/L (0.13–0.36), C1 inhibitor 0.25 g/L (0.14–0.4) and CH 50 titer > 50 % (> 50 %). IgE food and inhalants panels were negative, and the otorhinolaryngologist therefore referred the patient to the allergology clinic to be assessed for systemic mastocytosis, hereditary angioedema and anaphylaxis. We suspected that the attacks might be triggered by mast cell activation, and noted that they met the criteria for anaphylaxis (1) with their combination of hypotension, tachycardia, abdominal pain and generalised skin reaction. Neither the anamnesis, nor tests covering a broad spectrum of hidden allergens, revealed any specific trigger. Skin-prick testing for standard food and respiratory allergens was negative, and there were no cofactors, such as exertion, alcohol consumption or the use of non-steroidal anti-inflammatory drugs (NSAIDs), associated with the attacks.

A notable proportion of patients who experience anaphylaxis will show an acute increase in tryptase levels, and this is the biochemical gold standard for distinguishing anaphylaxis from similar conditions (2). The patient was asked to obtain a measure of her serum tryptase levels 1–4 hours after an attack, and she was given a note to present to her GP or to an Accident and Emergency department requesting that a sample be taken. One week later, she had another attack and her tryptase levels were measured acutely at 26.9 mcg/L, corresponding to a significant increase. A significant increase is defined as acute tryptase ≥ (basal tryptase × 1.2) + 2. After 24 hours, her tryptase levels had fallen to 17.9 mcg/L. On the basis of the increase in tryptase immediately after the attack, the patient was diagnosed with idiopathic anaphylaxis.

The patient was informed about her condition and is now taking a high-dose antihistamine (loratadine 40 mg) and leukotriene receptor antagonist (montelukast 10 mg). She has also been equipped with an adrenaline auto-injector and has been trained in its use. The patient was given the adrenaline auto-injector only after receiving a firm diagnosis, but in retrospect she could have been given one as soon as it became clear that her attacks met the criteria for anaphylaxis. However, the overall clinical picture remained uncertain prior to the acute tryptase measurements that confirmed the diagnosis. Since starting treatment, the patient has been symptom-free and is being followed up by our outpatient clinic. She was considered fit to drive, as her attacks have always come on gradually with warning signs.

Discussion

Idiopathic anaphylaxis is a diagnosis of exclusion, and accounts for 6.5–35 % (3) of all episodes of anaphylaxis. Less than 1 % of anaphylactic attacks are fatal (4), but unfortunately it is not possible to predict the severity of anaphylaxis for an individual patient owing to the many cofactors that can influence severity (e.g. alcohol, illness, exercise, medications). Several other diseases are clinically similar to anaphylaxis, but the combination of hypotension and tachycardia, and the presence of symptoms in at least two organ systems should raise suspicion of anaphylaxis. Anaphylaxis often causes an acute increase in tryptase levels, and this can be used to diagnose the condition. Idiopathic anaphylaxis is a mast cell activation syndrome (5), in which the patient meets the clinical criteria for anaphylaxis and shows a measurable increase in tryptase levels during attacks with a return to baseline afterwards. Factors that support the diagnosis include a response to treatment with antihistamines and an effect of adrenaline.

Allergy testing with a broad spectrum of allergens is recommended to rule out any specific triggers. Between 65 and 90 % of patients go into spontaneous remission after a few years (6). In the absence of any definite triggers that can be avoided, the patient must be equipped with an adrenaline auto-injector for use in treating severe attacks and must be trained in when and how to use it. They should receive prophylaxis with non-sedating antihistamines, leukotriene antagonists and, if indicated, cortisone. Our patient had gone five years without a diagnosis and was relieved to receive an explanation for her symptoms. In retrospect, some of her episodes had been severe enough to warrant use of adrenaline, but most had been mild. The measurement of acute tryptase levels within 1–4 hours of an attack, as recommended (7), was crucial for her diagnosis. Tryptase measurement has recently been discussed in the Journal of the Norwegian Medical Association (2) and the current case report serves as a reminder of the importance of performing the right test at the right time.

The patient has consented to the publication of this article.

The article has been peer-reviewed.

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