

Exercise-Induced Anaphylaxis in an Air Force Aviator Taking a HMG-CoA Reductase Inhibitor: A Case Report and Review of the Presentation, Diagnoses, and Treatment

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ABSTRACT Background: A 46-year-old healthy male Air Force pilot presented to the emergency department (ED) experiencing symptoms of exercise-induced anaphylaxis (EIAN), during a vigorous outdoor run. The patient recovered in the ED and was seen, subsequently, by a civilian allergist; eventually a diagnosis consistent with EIAN was made. EIAN is a rare but potentially life-threatening syndrome believed to involve IgE mediated release of histamine and other immunoactive compounds, during or after exercise. The diagnosis is determined by a strong clinical suspicion along with careful exclusion of other potential diagnoses. Interestingly, this particular patient was also found to have a possible correlation between the introduction of 3-hydroxy-3-methylglutaryl-coenzyme A, for hyperlipidemia, shortly before his first episode of EIAN, and remission of the condition since discontinuing the statin medication. Methods: A detailed review of the clinical notes, ED presentation, and all subspecialty consultation notes were included in the compilation of this case report, in conjunction with a careful review of all current literature pertaining to drug exacerbated, exercise-induced EIAN. The review of literature was also conducted to review potential mechanisms of this particular hypersensitivity reaction, and to give a thorough discussion of the history and presentation of this disorder. Results: The patient described in this case was successfully treated over a 2-year period, with exercise modifications and a daily second generation antihistamine. Nearly a year after his initial diagnoses, in an acute visit to the flight medicine clinic for muscle soreness and elevated creatine kinase isoenzymes, the patient's medication profile was reviewed and his statin medication was discontinued. The clinical notes revealed that the statin was started a few months before his first onset of EIAN, and following its discontinuation, the patient has been asymptomatic for over a year, exercising regularly, and completed a successful forward deployment to an austere desert environment. Discussion: To our knowledge, this is the first reported case of possible statin exacerbated, EIAN. Data concerning the incidence of drug-induced hypersensitivity to statins are limited as is any discussion on prevalence of EIAN in adult populations. There have been, however, case reports documenting statin immunological effects on serum IgE levels, which may offer a potential mechanism of statin-exacerbated EIAN. However, the role of IgE antibodies in drug-induced anaphylactic reactions remains unclear. In this patient's case, there was no measure of statin-specific immune reactivity performed; however, the timing of statin initiation of monotherapy in relation to presentation of EIAN strongly supports the diagnosis of statin-exacerbated EIAN. Although the mechanisms involving statin-induced EIAN remain elusive, this case report illustrates the need for military providers to recognize this condition and cofactors that may contribute to its genesis. Moreover, this case also illustrates the need for increased research and surveillance of this condition in civilian and military populations.

INTRODUCTION

Exercise-induced anaphylaxis (EIAN) is a rare but potentially life-threatening syndrome. It presents with signs and symptoms that occur during or shortly following exercise. Signs and symptoms include sudden fatigue, warmth, pruritus, flushing, and urticaria and may progress to anaphylactic shock including upper airway compromise secondary to bronchospasm or circulatory collapse. A strong clinical suspicion, exclusion of other potential diagnoses, and a meticulous clinical history are required for diagnosis. The history includes character and intensity of exercise, as well as environmental variables, and it may also elucidate triggers—including temperature or medications. Treatment is primarily antihistamines, avoidance, never exercising alone, and immediate access to an epinephrine auto-injector (EpiPen; Meridian, St. Louis, Missouri).

CASE REPORT

A 46-year-old active duty male KC 10 pilot with over 3,000 flying hours presented to the flight medicine office to be considered for a U.S. Air Force Flying Class II waiver, for a history suspicious for EIAN. The first episode occurred a few months earlier during his drive home after exercising; he noticed tongue and lip swelling with a pruritic “hive-like” rash over his arms and extremities. He was seen at local ED, given a liter of normal saline along with 125-mg intravenous methylprednisolone and 50-mg of intravenous ranitidine. On follow-up with a civilian allergist, it was revealed that he had undergone immunotherapy for pollen and allergic rhinitis several years prior. He had a negative brain magnetic resonance imaging and normal pulmonary function tests and an unremarkable IgE panel; at that time he was confirmed likely to have EIAN, the patient was given instruction to exercise with a partner and carry an EpiPen. The patient suffered another attack a month later, where he had similar symptoms as his first episode about 15 minutes after running two 9-minute miles. The hives returned on thorax, neck, and arms; however, there was no syncope, hypotension, blurred vision, wheezing,

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and shortness of breath. He received diphenhydramine and methylprednisolone intramuscularly at an urgent care center and his symptoms resolved. Given the unpredictable and potentially lethal nature of EIAN, the patient was once again advised to avoid running long distances, carry an epinephrine auto-injector at all times, and to run with a partner. After another review by his civilian allergist, it was found that the symptoms and blood analysis were not consistent with food or environmental triggers. He was eventually cleared to return to fly after subspecialty approval and a flying class IIC waiver was granted. During the record review process for an operational waiver to deploy for 1 year to a base in southeast Asia, he had an episode of persistent symmetrical lower extremity pain for several days after a workout. Creatine kinase isoenzyme was found to be elevated, and it was noted by the flight surgeon that many of his symptoms of EIAN began a short time after starting Simvastatin. At that time the statin was discontinued; since removal he has been asymptomatic for nearly a year, exercising at full capacity regularly and forward deployed in an austere desert environment without any relapse of EIAN.

DISCUSSION

EIAN is characterized by signs and symptoms of anaphylaxis in the setting of physical exertion.^{1,2} Symptoms may begin at any stage of exercise and occasionally occur just after exercise.^{3,4}

Many patients engage in regular exercise without consistent reproducibility of signs or symptoms as listed in Table I; however, some experience a single episode of anaphylaxis over years of exercise and others experience monthly or even more frequent episodes.⁵ Most patients exercise for years before experiencing their first episode.

There is some evidence to suggest certain exposures may increase the likelihood of developing EIAN, including non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, high heat or humidity, and cold exposure.^{6,7}

Although EIAN is considered rare, the data for prevalence and incidence of EIAN among adult populations are

scarce.^{8–12} A recent epidemiological study involving 76,229 junior-high-school students in Japan found that the frequency of EIAN and food-dependent EIAN was 0.031% and 0.017%, respectively. They also found no difference between sexes.¹³

The pathophysiology of EIAN is not completely understood; however, mast cell degranulation with subsequent histamine release is thought to play a primary role. Although the specific events responsible for mast cell activation are unknown, an association between mast cell degranulation, vasoactive mediators (including elevated plasma histamine), and EIAN exists.^{5,14–17} Other proposed potential mechanisms include exercise-induced changes in blood flow, antigen presentation, blood pH, and gut permeability.^{15,17} Gastrin is among the mast cell secretagogues known to be released during exercise.¹⁸

EIAN is a diagnosis of exclusion. A meticulous clinical history should be obtained and other potential diagnoses should be excluded. The differential includes cold-induced urticaria and anaphylaxis, exercise-induced asthma, cholinergic urticaria, mastocytosis, and food-dependent exercise-induced anaphylaxis.

In EIAN, exercise challenge testing is not required for diagnosis. Given the lack of validated exercise protocols and the lack of reproducibility of symptoms, exercise testing is often not performed.³

Treatment of EIAN is preventative, largely by avoidance, as there are no randomized controlled trials of therapy, other identified triggers such as NSAIDs, high humidity or heat, and alcohol should also be avoided.

Prophylactic pharmacotherapy has not been systematically studied; however, there are published case reports and rationalized empiric treatments. Some small trials have suggested a benefit from daily antihistamine prophylaxis. Other therapies reported but not systematically studied include leukotriene inhibitors, misoprostol, and oral corticosteroids.^{19,20}

In this particular case report, we have suggested a presumptive statin exacerbated EIAN because of the immediacy of symptomology following the introduction of simvastatin, and the resolution of the condition since its discontinuation. Simvastatin is a potent lipid-lowering agent in the class of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly referred to as statins. As a class, statin agents are widely used because of their established clinical benefits and favorable side effect profile.^{21,22} The most commonly documented adverse effects of statin therapy are myopathy and increased liver transaminases, with overall clinical evidence suggesting severe cases of liver dysfunction and rhabdomyolysis are rare.^{23–25}

Data concerning the incidence of drug-induced hypersensitivity to statins are limited. Liebhaver et al²⁶ described 10 case reports of statin-induced hypersensitivity in a multispecialty clinic, with episodes characterized by urticaria, angioedema, pneumonitis, exertional dyspnea, and worsening left ventricular function. A hypersensitivity-type reaction has also been reported by a 70-year-old male with asthma-like symptoms,

TABLE I. Signs and Symptoms of Exercise-Induced Anaphylaxis (EIAN)

Diffuse warmth and/or flushing
Generalized pruritus
Urticaria (hives are usually 10–15 mm in diameter or larger, rather than the “punctate” hives normally seen in cholinergic/heat-induced urticaria)
Sudden fatigue
If exercise continues, there is a progression to more severe symptoms, including one or more of the following:
Angioedema of the face and/or extremities (often the hands)
Gastrointestinal symptoms, including nausea, abdominal cramping, and diarrhea
Laryngeal edema
Hypotension and/or collapse
Bronchospasm is reported in some patients, although it may be less common in EIAN than in anaphylaxis from other causes ^{1–3}

REFERENCES

urticaria, angioedema, and an elevated serum IgE level after exposure to lovastatin and pravastatin.²⁷ De Jong et al²⁸ identified a trend toward increased levels of IgE antibodies in patients on statin therapy; however, the clinical utility of this finding is not known. Although statins have well-documented immunomodulatory properties, the potential mechanism of statin-induced hypersensitivity reactions is unknown.^{29–31}

To our knowledge, there are no published reports of EIAN associated with the use of a statin. NSAIDs are the only pharmacologic agents with a described role as a trigger for EIAN, because of the effects on increasing intestinal permeability.³² There are no data which describe statin involvement with intestinal permeability. There are reports on the immunological effects of statin agents in preventing mast cell degranulation; however, no reports on influencing degranulation or histamine release.^{33,34} Taken together, these observations provide considerable reason to believe the mechanism of statin exacerbated EIAN relies other drug-induced processes. The association of statin use and increased levels of IgE may offer a potential mechanism of statin exacerbated EIAN. However, it is important to note that the role of IgE antibodies in drug-induced anaphylactic reactions is debated.^{31,35,36}

Although no measure of statin-specific immune reactivity was performed in this case, the patient's medication regimen consisted of statin monotherapy during the described case. The timing of statin initiation before the patient presentation of EIAN strongly supports the assessment of statin exacerbated EIAN. It is unclear, in this case, of the potential mechanism of the reaction.

CONCLUSION

EIAN is a rare but potentially life-threatening syndrome presenting with signs and symptoms of anaphylaxis during or shortly after exercise. It is a clinical diagnosis of exclusion confirmed by a meticulous history. Treatment is primarily avoidance of identified triggers, exercising with a partner trained in sign and symptom recognition as well as administration of an epinephrine auto-injector, and prophylactic pharmacotherapy for potential reduction in severity. If the patient presents with signs or symptoms of anaphylaxis or anaphylactic shock, treatment is the same as conventional therapy (e.g., epinephrine, etc.). A graded exercise program should be undertaken to ascertain a safe level of exercise. EIAN is unpredictable and extreme caution should always be advised. Other medications may be implicated in EIAN and should be evaluated on a case by case basis. In this particular patient, it is compelling that the symptoms started a few months after starting simvastatin, and have completely resolved now 1 year after discontinuation of the drug. Since statins are commonly used agents for lipid management and cardiovascular disease prevention, it is important for prescribers and pharmacists to be aware of less obvious, delayed reactions that may occur during therapy. This is especially true in military operators where austere environments and high-intensity exercise is the norm.

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