Idiopathic anaphylaxis The hidden allergy?

Keywords: Allergy, anaphylaxis, Food allergy

Most people have heard of severe allergies, or anaphylaxis, to food, insect stings, drugs and other common substances, but sometimes no cause at all can be found for a person's reaction – a condition called Idiopathic anaphylaxis. But does this really mean they are reacting to nothing?

To raise awareness of this little known condition and help those affected, the Anaphylaxis Campaign has updated its factsheet on Idiopathic anaphylaxis.

Anaphylaxis is the most severe form of allergic reaction and can be fatal in the worst cases, yet is more common than you might think. Food allergy alone is thought to affect 1 – 2% of the adult population and 4–6% of children and there are estimated to be around 30,000 cases of hospitalisation due to anaphylaxis every year. In some cases, these reactions will be termed idiopathic, as even after intense diagnostic investigation, no discernable cause can be found.

Symptoms may begin suddenly and progress quickly, ranging from mild nettle rash, tingling or itchy feeling in the mouth, to severe swelling of the face, throat or mouth, breathing difficulty, severe abdominal pain, nausea, vomiting and in extreme cases there could be a dramatic fall in blood pressure (anaphylactic shock). This causes weakening and floppiness and may cause a sense of impending doom in the patient. Collapse and unconsciousness can follow and reactions of this severity may even prove fatal if not treated promptly with adrenaline.

So what is behind Idiopathic anaphylaxis?

This curious and frustrating diagnosis can occur for two main reasons. Firstly, no trigger can be identified because, while an external trigger (such as a food) might be present, tests may fail to pick it up. Secondly however, it could also mean that there is no external trigger at all and the cause is a temporary
increase in the reactivity of the body's immune system. If an external trigger is present, it may be one of a few possibilities, including:

Food – this should be considered a prime suspect, especially foods eaten shortly before the start of an attack

Lupin – the seeds from some varieties of lupin are milled to make flour, which is used in baked goods such as pastries, pies, pancakes and in pasta

Latex – found in thousands of everyday consumer and healthcare items, with allergy to latex becoming increasingly common over the past 25 years

Flour contaminated by mites – this condition is known colloquially as Pancake Syndrome; the medical term is Oral Mite Anaphylaxis, with anaphylaxis occurring shortly after the intake of foods made with mite-contaminated wheat flour

Cold induced urticaria/anaphylaxis – in rare cases, anaphylaxis can be caused by chilling. For example, a nine-year-old girl suffered urticaria (hives all over her body) and lost consciousness while swimming in cold water. She was immediately removed from the water and regained consciousness. She had a preceding two-year history of multiple episodes of urticaria while swimming in unheated water (Fernando SL, 2009)

What can be done?

Moira Austin, Helpline Manager for the Anaphylaxis Campaign said; "Our factsheet on Idiopathic anaphylaxis will shine a light for many on their condition, as there is almost nothing out there for patients who receive this diagnosis. This can be an upsetting, as it provides no closure and means people cannot practice avoidance – one of the key means of managing anaphylaxis – because they simply do not know what they should be avoiding."

Dr Michael Radcliffe, a member of the Anaphylaxis Campaign's Clinical and Scientific Panel, helped produce the factsheet and said: "If allergy-like symptoms are present but the cause is a mystery, it is important that a detailed account is kept, noting time, date, location, consumption and activity in the hours leading up to the reaction. All these details might help to build a picture of the problem and possibly identify a common thread."
Idiopathic anaphylaxis: The facts

Anaphylaxis is a severe allergic reaction – the extreme end of the allergic spectrum. Causes include food, insect stings, latex and drugs. But sometimes there may be no obvious trigger. If, after a diagnostic investigation, no cause can be found, the anaphylactic reaction is termed idiopathic. This does not necessarily mean the reaction took place without something triggering it – but simply that no trigger can be identified. It might mean that there is an external trigger (such as a food), but tests fail to pick it up. However, it can also mean that there is no external trigger and the cause is a temporary increase in the reactivity of the immune system. This increased reactivity usually clears up within a few weeks or a few months, although in some cases the condition may take a year or two to settle. A key message in all cases is to visit your GP and ask for a referral to an NHS allergy specialist.

This factsheet aims to answer some of the questions that you and your family might have if you are diagnosed with idiopathic anaphylaxis. Our aim is to provide information that will help you understand your allergy and minimise risks.

Throughout the text you will see brief medical references given in brackets. More complete references are published towards the end. Anaphylaxis can be a life-threatening condition, but you can be assured that you can manage the condition successfully so long as you have high-quality medical guidance and always carry prescribed medication.

Symptoms of anaphylaxis
Mild symptoms may include nettle rash (also known as hives or urticaria) anywhere on the body, or a tingling or itchy feeling in the mouth. There may be facial swelling, which is not serious in itself unless any of the more severe symptoms listed below are also present.

More severe symptoms may include:
- Swelling in the throat and/or mouth
- Difficulty breathing
- Severe asthma
- Severe abdominal pain, nausea and vomiting

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In extreme cases there could be a dramatic fall in blood pressure (anaphylactic shock). The person may become weak and floppy and may have a sense of something terrible happening. This may lead to collapse and unconsciousness. The speed at which life-threatening symptoms occur varies from person to person. Symptoms may begin suddenly and progress quickly.

In general, the first episode of idiopathic anaphylaxis tends to be the most frightening because the person affected has no understanding what is happening or what to do about it. After that, they may recognise the initial symptoms and act quickly.

Getting a diagnosis

It is important to see your GP as soon as possible if you suffer any symptoms that you think may be caused by an allergy. Even apparently mild cases need to be medically assessed because your next reaction could be more severe. Some GPs have a clear understanding of allergy and similar conditions, but it’s more likely your doctor will need to refer you to an allergy clinic. Guidance issued by the National Institute of Health and Care Excellence (NICE) recommends that following emergency treatment for suspected anaphylaxis, people should be offered referral to a specialist allergy service. (NICE clinical guideline 134, 2011). Your GP can locate an allergy clinic in your area by visiting the website of the British Society for Allergy and Clinical Immunology (www.bsaci.org).

Once you get a referral, the consultant will discuss your symptoms with you in detail as well as your medical history. The results of skin prick tests and blood tests may help the specialist identify the cause of the problem. If no cause can be found then the term idiopathic anaphylaxis is used. Sometimes the cause of the first attack may not be obvious but the trigger can become clear with subsequent attacks.

Food should be considered as a prime suspect. Foods eaten a few minutes before the start of an attack are the most likely culprits. It is less likely that a food eaten more than an hour before the start of an attack will have been the cause. The most common food triggers are shellfish, fish, peanuts, tree nuts (such as cashews, walnuts or Brazils), milk, eggs and wheat, but many others are also implicated on rare occasions. If a particular food is suspected, but skin
or blood tests are unexpectedly negative, the consultant may suggest an oral food challenge test to eliminate this food.

Prescribed drugs, insect stings and latex may also be considered as the cause of the reaction. Any medication taken for years may suddenly cause anaphylaxis. If skin tests are not available for a suspected medication, you may be required to exclude it temporarily and then take a test dose. This must be done under supervision in hospital.

A diagnosis of idiopathic anaphylaxis should only be made after an extensive medical investigation. This should include a review of all hospitalisation and A&E records.

Treating symptoms
So you can treat severe symptoms yourself, your doctor is likely to prescribe injectable adrenaline (also called epinephrine). You may also be prescribed an antihistamine.

The adrenaline injectors prescribed in the UK at present are Emerade®, EpiPen® and Jext®. These injectors are easy to use and designed for self-administration.

If you are prescribed an injector, it should be available at all times – with no exceptions.

If you are prescribed an adrenaline injector, you will need to know how and when to use it. Ask your GP or allergist for advice. You can also find help on the website relevant to the injector you carry.

After adrenaline is administered, someone must always dial 999 in case the symptoms return. Guidelines state that you should lie flat with your legs raised (Resuscitation Council UK, 2008). If you feel as though you may be sick, your head should be turned to one side.

If the symptoms of a previous attack of anaphylaxis progressed rapidly, you will probably be advised to use the injectable adrenaline at the first unmistakable
sign of an attack. If the symptoms of previous attacks progressed more slowly, you may be advised to take an antihistamine when mild symptoms occur (such as lip tingling, itchy mouth or itchy hands) and reserve injectable adrenaline until the first sign of the more severe symptoms. It is important to obtain guidance on these points from your allergy consultant.

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If you suffer from asthma – especially if it is poorly-controlled – the risk of any allergic reaction being severe will be higher. If you have asthma, go to your GP and request a review of your asthma to ensure that you are using the most effective treatment.

As stated in our introduction, some cases of idiopathic anaphylaxis have an internal cause – a temporary increase in the reactivity of the immune system. Cases in which attacks are occurring frequently may require a few weeks or months of regular treatment such as a daily oral steroid to prevent further attacks and help the condition to settle down. Anaphylaxis may occur for up to two years before finally burning itself out.

We advise people who have experienced anaphylaxis – whether or not the cause is known – to wear a medical identification bracelet or talisman.

Finally, we believe it is important to let your family, friends or work colleagues know where you keep your adrenaline injector and what needs to happen in an emergency. In the case of children, the school will need a written care plan.

Emergency treatment of anaphylaxis – what injectors are available?
Pre-loaded adrenaline injection devices – Emerade®, EpiPen® or Jext® – are available on prescription for those thought to be at risk of a severe reaction. Emerade® is the most recent single use adrenaline auto-injector to become available. It has a needle guard to protect against needle stick injury. Visit www.emerade.co.uk

EpiPen® has a spring-loaded concealed needle. The built-in needle protection keeps the needle covered during and after use. Visit www.epipen.co.uk.

Jext® has a locking needle shield which engages after use, designed to protect against needle injury. Visit www.jext.co.uk.
A few possible causes
When someone suffers a suspected allergic reaction, they may be tempted to consider one of the common food allergens as the culprit, such as peanut or shellfish. Indeed this may prove to be the case, either because the allergen was present in the food eaten or because of cross-contamination somewhere in the food production process. However, the cause of the problem may be less obvious. A few possibilities are presented here.

Lupin: The seeds from some varieties of lupin are milled to make flour, which is used in baked goods such as pastries, pies, pancakes and in pasta. Allergy to lupin has been recognised for some time in mainland Europe, where lupin flour is used fairly commonly in food products. In the UK, cases of lupin allergy are less common because lupin is rarely used in foods. If you suffer an allergic reaction and discover that lupin was present in a food you have eaten, you might consider this as the possible trigger. By law, lupin must be declared in the ingredients list when present in pre-packed food.

Natural Rubber Latex (NRL): This is found in thousands of everyday consumer and healthcare items. Reports of allergy to Natural Rubber Latex have become increasingly common over the past 25 years and severe reactions occur quite frequently. Many people associate allergy primarily with food – but latex should be considered as a possible cause if a reaction occurs during an operation, during a medical or dental procedure, or just after handling an item made of soft rubber.

Flour contaminated by mites: In 2009 the World Allergy Organisation (WAO) published information on allergy to wheat flour contaminated with mites. The condition is known colloquially as Pancake Syndrome; the medical term is Oral Mite Anaphylaxis. According to the WAO paper (Sánchez-Borges et al, 2009), Oral Mite Anaphylaxis occurs shortly after the intake of foods made with mite-contaminated wheat flour. The condition is seen most frequently in tropical or subtropical environments, but cases are occasionally seen in the UK. Reactions
The oleosins in sesame: A research team reported that proteins called oleosins, which are major allergens of sesame seeds, accounted for about third of all cases of sesame allergy among the people they studied. However because oleosins do not dissolve in water (in the sesame seed, they exist in intracellular oil globules), they cannot be identified by allergy skin or blood tests (Leduc et al 2006). Therefore an allergy could mistakenly be classed as idiopathic when the true cause is sesame seeds. To address this problem, an oral food challenge test may be used for cases where sesame allergy is suspected but cannot be proved. Exercise induced anaphylaxis (EIA): This is an uncommon condition in which anaphylaxis occurs after physical activity. It is potentially serious for people affected and requires expert diagnosis. If you think you suffer from EIA, the best course of action is to ask your GP to refer you to an NHS allergy clinic. EIA can also occur in combination with other factors such as a food (see below under the section headed “More than one trigger?”). Cold induced urticaria/anaphylaxis: In rare cases, anaphylaxis can be caused by chilling. For example, a nine-year-old girl suffered urticaria (hives all over her body) and lost consciousness while swimming in cold water. She was immediately removed from the water and regained consciousness. She had a preceding two-year history of multiple episodes of urticaria while swimming in unheated water (Fernando SL, 2009). Patients who suffer from cold urticaria will develop hives when their skin is chilled by cold rain, cold water or cold weather. If you think you suffer from cold urticaria, you may be at risk of cold anaphylaxis and the best course of action is to ask your GP to refer you to an NHS allergy clinic. More than one trigger? For a small minority of people, anaphylaxis can occur when a combination of factors are present together. This makes diagnosis difficult and without a thorough investigation the symptoms may be classed as idiopathic. Here we give a few examples taken from the medical literature.
Food plus exercise: This is called food–dependent, exercise induced anaphylaxis (FDEIA). The symptoms occur when a food is eaten before exercise. Wheat is often the culprit food, although others including shellfish are sometimes implicated. Looking at the available evidence, we believe that anyone diagnosed with FDEIA should avoid exertion for 12 hours after eating their trigger food. It would be safer to avoid the food altogether even if it is normally not a problem without exercise. There have also been rare reports of symptoms occurring when the food is eaten immediately after exercise.

Food plus exercise and aspirin: A research team examined a patient with a history of FDEIA related to eating wheat before exercise. They found that he also suffered a reaction when aspirin was taken before eating wheat – even without exercising. The combination of aspirin, wheat and exercise triggered symptoms that were even more severe. Wheat alone did not trigger symptoms (Harada et al, 2001). The same report describes the case of an 18–year–old man with FDEIA who suffered symptoms with a combination of aspirin, shrimp and subsequent exercise. In other cases ibuprofen and other non–steroidal anti–inflammatory drugs (NSAIDs) may act as the responsible co–factor.

Exercise and exposure to cold: Researchers reported on a 16–year–old Japanese boy who had a four–year history of allergic reactions when he exercised in winter. Tests showed it was the combination of cold and strenuous exercise that triggered the symptoms. Food was not thought to be a factor in this case (Li et al, 2002).

Cereal mites with exercise: A 17–year–old boy suffered anaphylaxis while jogging after having eaten a Japanese pancake. The pancake mix, which had been stored for several months after the package had been opened, was examined under a microscope, and an abundant number of live mites were discovered. The researchers concluded that it was ingestion of mites associated with exercise that caused the symptoms (Adachi et al, 2013). One of our medical advisers tells us he saw the case of a boy who exercised in the snow
after eating a breakfast cereal from a packet which had been open for many months. The boy suffered a severe anaphylactic reaction.

- Intolerance to non-steroidal anti-inflammatory drugs (NSAIDS): Painkillers such as aspirin and ibuprofen should also be regarded as a possibility when the cause of an allergic reaction is a mystery.

Diseases that mimic anaphylaxis

Angioedema is a condition similar to anaphylaxis. In angioedema, there are recurring episodes of painless swelling that may involve the lips, face (especially around the eyes) tongue, upper airway or anywhere in the body. In many cases no cause for these symptoms can be identified and the attacks stop happening after a few weeks or months. When attacks are persistent, the most common identifiable cause is a side-effect of ACE inhibitors, which are prescribed to treat blood pressure problems. According to research, this treatment causes occasional attacks of angioedema in about 1 person in 300 who takes it (Makani et al, 2012). As the attacks may not start for several months after the treatment has begun, this possibility may be overlooked.

Note that although angioedema is a condition in its own right, it can also occur during anaphylaxis.

Hereditary angioedema is a rare, inherited, non-allergic form of angioedema. In addition to external swelling, there may also be stomach cramps, abdominal pain, nausea and diarrhoea. The episodes may follow localised injury such as dental work. The angioedema (swelling) tends to be painful and slow in onset. This disorder can be differentiated from non-inherited angioedema and anaphylaxis by blood test findings and the lack of other symptoms of anaphylaxis.

Histamine poisoning: Histamine can sometimes be present in spoiled fish (especially tuna and mackerel) and can cause a condition not unlike allergy called scombroid poisoning. Unlike an allergy, this usually affects everyone who has eaten the offending food, although some people might be more susceptible than others.
Mastocytosis: This is a rare condition caused by too many ‘mast cells’ gathering in the tissues of the body. These are the cells that release histamine and other chemicals involved in allergic reactions, causing symptoms such as a skin rash, itchy skin and anaphylaxis. If you have this condition, it’s important that your doctor identifies mastocytosis as the cause of your symptoms.

Tips and advice
If you suffer allergy-like symptoms but the cause is a mystery, keep a detailed account of your experience. Important points to note down are:

- Where you were at the time of the reaction
- The time of day
- What you had eaten or drunk within the hours leading up to the reaction
- Whether you had taken a painkiller or other medication within a few hours before the reaction
- Whether you were taking a medication known to be associated with allergic reactions
- Your general state of health
- Whether you were particularly hot, cold or stressed
- Whether you had been exercising at the time of the reactions or just before

All these details might help to build a picture of the problem and possibly identify a common thread.

Some other things to consider:
- Do you suspect that a food is responsible? If so, try to get a detailed list of the ingredients of any foods, sweets or snacks eaten within the hour before the reactions.
- If a takeaway or restaurant meal is suspected, it will help your doctor find a cause for the reaction if you obtain a full list of the ingredients.
- Have you considered latex as a possible trigger?
- Have you considered a medication as a possible trigger?


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Reviewers
The content of this Fact Sheet has been Peer Reviewed by Dr Michael Radcliffe, Consultant in Allergy Medicine, University College London Hospitals NHS Foundation Trust; and Prof John Warner, Professor of Paediatrics and Head of Department, Imperial College, London.

Disclosures
Both Dr. Radcliffe and Prof. Warner are members of the Anaphylaxis Campaign’s clinical and scientific advisory board.

Disclaimer – The information provided in this Factsheet is given in good faith. Every effort has been taken to ensure accuracy. All patients are different, and specific cases need specific advice. There is no substitute for good medical advice provided by a medical professional.

About the Anaphylaxis Campaign: Supporting people with severe allergies
The Anaphylaxis Campaign is the only UK wide charity to exclusively meet the needs of the growing numbers of people at risk from severe allergic reactions (anaphylaxis) by providing information and support relating to foods and other triggers such as latex, drugs and insect stings. Our focus is on medical facts, food labelling, risk reduction and allergen management. The Campaign offers tailored services for individual, clinical professional and corporate members.
Visit our website www.anaphylaxis.org.uk and follow us on Twitter @Anaphylaxiscoms.