

Rare and Uncommon Diseases

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Edited by

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CHAPTER ONE

ADDISON'S DISEASE

MUHAMMAD IMRAN QADIR

Summary

Addison's disease is a rare but dangerous endocrine disease in which the adrenal glands do not produce the appropriate type and/or amount of steroidal hormones. Blood tests and imaging are generally used to diagnose it. Nausea and vomiting are common symptoms of the disease. In Addison's disease, continued steroidal hormone replacement treatment is needed.

Keywords: Addison's disease, Hyperglycemia, Autoimmune disorder, Hydrocortisone tablets, Hypocortisolism, Hyperpigmentation, Adrenal gland

Introduction

Addison's disease is due to severe or total destruction of the adrenal glands.¹ The glands have two parts; the medulla and the adrenal cortex. Epinephrine and nor-epinephrine are not involved in Addison's, but the cortical hormone and aldosterone are.

In Addison's disease, secretion of the glucocorticoid, a cortical hormone, becomes very limited, and aldosterone (which is a mineralocorticoid) secretion is inhibited completely.

Addison's disease got its name from a British physician, Dr. Thomas Addison. He explained the condition with reference to its local effects on the suprarenal capsule.² The characteristics of the condition and of those who suffer from Addison's disease are described as Addisonian. Blood tests and imaging are used in its diagnosis.³

Symptoms

It was previously thought that Addison's is a chronic disease. Its symptoms proceed slowly, and its diagnosis is a lengthy process. In 1855, many Addison's patients were also found to be suffering from adrenal tuberculosis.⁴ Commonly described symptoms of this disease include severe fatigue, weight loss, skin pigmentation, low blood pressure, nausea, vomiting, salt cravings, pain in the muscles and joints, low blood sugar levels (hypoglycemia) and irritability. Darkening does not start in a patient suffering from Addison's disease until the adrenal deficiency fails to be compensated for in the skin layer by hyper-pigmentation.⁵ Blood sugar levels fall when the patient suffers from Addison's disease unremittingly. The pinna of the ear may become obstructed. Characteristic symptoms include sudden pain in the legs, lower back or abdomen, and acute diarrhea, amongst others.

Causes

Causes for adrenal deficiency are grouped in several ways. These include adrenal dysgenesis (where the gland has not developed well and produces insufficient amounts of cortisol), impaired steroid genesis (where the gland's secretion is inhibited although it is intact), or destruction of the adrenal glands.

Adrenal dysgenesis is an important genetic cause of Addison's disease. Mutation occurs in the congenital hyperplasia due to DAX-1 gene mutations and mutations in the ACTH receptor gene (or related genes, such as in the triple A or Allgrove syndromes).⁶ Mutations of DAX-1 may bundle a syndrome involving glycerol kinase deficiency with a number of other symptoms when DAX-1 is deleted along with a number of several other genes.

A less common cause of Addison's disease is autoimmune inflammation. Cortical damage occurs due to an immune reaction against the enzyme 21-hydroxylase.⁷ This may occur independently or in the context of autoimmune polyendocrine syndrome (APS type 1 or 2), in which other hormone-producing organs such as the thyroid and the pancreas may also be affected.⁸

The destruction of adrenal glands is also a characteristic of adrenoleukodystrophy (ALD), and when the adrenal glands are involved, haemorrhage, particular infections (tuberculosis, histoplasmosis, coccidioidomycosis), or the deposition of abnormal protein in amyloids may occur.^{9, 10}

Treatment

Replacing the missing hormones or substituting them by related hormones (hormones which are not produced by the glands) is the principal treatment for this disease. Hydrocortisone tablets replace the cortisol. Glucocorticoid which is taken once or twice a day.¹¹ Deficiency of the mineralocorticoid, i.e. aldosterone, is compensated for by taking fludrocortisone acetate once a day. Patients receiving aldosterone replacement therapy are instructed to gradually decrease the superfluous salt intake, because they are normally still producing aldosterone.

Low blood pressure due to the low sugar level in Addison's disease is life-threatening, therefore standard therapy involves intravenous injections of saline, hydrocortisone and dextrose. This is a treatment which brings about rapid improvement in cases where the patient cannot take medication orally. When the patient is able to take medication orally, oral doses of fludrocortisone acetate are used to maintain the hydrocortisone level.^{12, 13}

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CHAPTER TWO

ANAPHYLAXIS

MUHAMMAD IMRAN QADIR

Summary

Anaphylaxis is a serious allergic reaction among numerous other life-threatening allergic reactions, and is more harmful than any other. Complete tracheal constriction, anaphylactic shock and even death, may result from this allergic reaction; it is an unpredictable condition. A substance that stimulates an allergic response or allergic reaction is called an allergen. Low blood pressure, breathing problems and faintness are the major symptoms which may be fatal in some patients. The dose of the antigen, its distribution, and its route of entry are the factors determining the severity of the symptoms. The RAST test is used for the diagnosis of anaphylaxis. Epinephrine is used in the treatment of the disease.

Keywords: Allergic reaction, Anaphylactic shock, Allergens, Epinephrine, Auto injector

Introduction

Anaphylaxis (pronounced as an-a-fi-LAK-sis) is an acute life-threatening hypersensitivity allergic reaction.¹ Anaphylaxis, which is composed of two words, 'ana' (which means 'against') and 'phylaxis' (which means 'protection'), is a manifestation of hypersensitivity caused by the exposure to an antigen, resulting in severe breathing and cardiac problems.² It is mostly caused by foods, medications, and insect stings.

Alternative Terms

Anaphylaxis is also known as a hypersensitivity type 1 reaction, an anaphylactic reaction, or an anaphylactic shock.³

Pathophysiology

Anaphylaxis is a severe reaction. When the initial exposure takes place, or any foreign substance enters the body, then, under normal circumstances, immunity develops against that substance. Many types of antibodies are produced by B lymphocytes^{4, 5} which destroy the substances that the immune system has identified as pathogens.⁶ In the case of later exposure, a sudden allergic reaction may take place. It is a type of hypersensitivity which is triggered when an antigen or foreign particle binds to IgE (antibody type) attached to the mast cells. In susceptible individuals, antibodies may also be produced against allergens which are part of the food intake. Among these antibodies, IgE is responsible for anaphylaxis, and can be produced even in the case of an ion. These antibodies are attached to the surface of mast cells so they become major effectors for allergic reactions. They are large cells produced by the bone marrow^{7, 8} and have large granules that store molecules such as histamine, vasoactive amine, prostaglandin—C4 and TNF. These mediators cause many symptoms, like itching, swelling and hives. Histamine causes dilation of the blood vessels as well as smooth muscle contraction. The permeability of the capillaries increases, and blood pressure becomes uncontrolled. Anaphylactic shock may lead to a heart attack.⁹

Types of Anaphylaxis

Based on pathophysiology, anaphylaxis is divided into two types:

1. True anaphylaxis
2. Pseudoanaphylaxis

In both types, the symptoms, treatment therapies and risks of death are the same; the difference is that true anaphylaxis is due to deregulation of the mast cells whereas pseudoanaphylaxis is due to medicines.¹⁰

Causes

The following are some common causes of anaphylaxis:

Food: Many foods cause severe allergic reactions, but the major foods that may cause anaphylaxis are peanuts, shellfish, fish, tree nuts, milk, eggs and preservatives.^{11, 12}

Stinging insects: Being stung by honeybees, wasps, hornets, fire ants and horse flies can cause a severe type of anaphylaxis, which may even lead to death.^{13, 14}

Medicine: Many kinds of medicine can cause an allergic reaction. Common types of medicine that produce an allergy are antibiotics e.g. penicillin, streptomycin, and others include gamma globulins, insulin and aspirin.¹⁵

Latex: Many products that are made of natural latex may cause an allergic reaction.¹⁶ A severe reaction may occur when latex reacts with humid areas of the body during surgery or operations.

Exercise: On rare occasions, exercise may produce anaphylaxis. If a person consumes certain foods before exercising, an allergic reaction may occur, though not every time.¹⁷

Symptoms

Anaphylaxis is a life-threatening hypersensitivity reaction against antigens. This is mainly due to the release of histamine. The most common areas to be affected by this reaction are the skin, the gastrointestinal tract and the cardiovascular and nervous systems.¹⁸ General symptoms of the reaction include a tingling sensation, angioedema, hyperemia, and, in severe conditions, vascular subside, bronchial tremor, and distress. The dose of the antigen, its distribution and its route of entry into the body are the factors which determine the severity of the symptoms. Symptoms of anaphylaxis include breathing, circulation, and skin and stomach problems, amongst others.

Breathing problems accompanying anaphylaxis include squatness of inhalation (70%), esophagus stiffness, coughing, a high-pitched voice, throbbing of the upper body, difficulty in swallowing, a tickling sensation in the mouth or throat and nasal dankness.¹⁹

Circulation problems: Whitish or cobalt coloured blood, pulse rate reduction, idleness, blood pressure reduction, panic and lack of awareness.

Skin problems: Pimples, bumps, prickles, redness and irritation.

Stomach problems: Vomiting, cramps, diarrhea and queasiness.

Other symptoms: Nervousness; itching; cherry colored, wet eyes; irritability; crumpling of the uterus, etc. Blood pressure reduction, breathing problems and faintness are the major symptoms that may be fatal in some cases.

Diagnosis

Anaphylaxis is diagnosed based on the rapid development of symptoms in response to an allergen.²⁰ The RAST test, a blood test that identifies IgE reactions or antibody reactions to specific allergens may be used to diagnose the disease.²¹ For less severe anaphylactic reactions, skin tests may be used. A blood test for determining the tryptase level may also be used.²²

Problems in diagnosis

Anaphylactic symptoms are sometimes similar to the symptoms of other diseases, like severe asthma therefore, diagnosing anaphylaxis may be problematic. If anaphylaxis occurs, the level of the protein tryptase that is present in the circulatory system increases and by taking a sample of the patient's blood, this allergy can be checked for. However, in some patients, tryptase levels remain unchanged.

Treatment

A principle method for the management of anaphylaxis is epinephrine.²³ It is the only medication that completely treats anaphylactic allergic reactions. It is most effective when used before the reaction becomes severe. Inhalation of antihistamines and anti-asthmatic drugs cannot treat anaphylaxis as well as epinephrine can. Intravenous fluids are also required for treatment.²⁴

Self-Medication

Anaphylaxis sufferers must have at least one epinephrine auto-injector with them at all times and should be well informed on when and how to use it.

Removing the cause

Whenever possible, the causes of anaphylactic reaction should be removed. For example, if a person has been stung by an insect, the stinger

should be wedged with the edge of a credit card or coin so that no more venom is released into the skin.

Consultation

After injecting epinephrine, it is important to go to a hospital emergency department. Up to 20% of those experiencing an anaphylactic reaction have a late-phase reaction, which causes many problems and may lead to death.

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CHAPTER THREE

ANAEMIAS

MUHAMMAD IMRAN QADIR
AND ASMA NOOR

Summary

Anaemias are a group of diseases characterized by a decrease in either haemoglobin or RBCs, resulting in the blood's reduced oxygen carrying capacity. In microcytic anaemia, RBCs are smaller in size than normal red blood cells, while in macrocytic anaemia, RBCs are larger in size than normal cells. Aplastic anaemia is due to the loss of function of the bone marrow. Haemolytic anaemia is due to increased destruction of the RBCs (haemolysis). Polycythaemia is characterized by an increase in RBC production.

Keywords: Haemolysis, Sideroblastic anaemia, Pernicious anaemia, Hereditary elliptocytosis, Hyperplasia

Introduction

Anaemia is derived from two Greek words; 'an' which means 'absence' and 'haima' which means 'blood'.¹ Anaemias are a group of diseases characterized by a decrease in either haemoglobin or RBCs, resulting in the reduced oxygen carrying capacity of the blood. The anaemic condition may be due to either a certain pathological or genetic cause. Sometimes, nutritional imbalance also leads to anaemia.

Types of Anaemia

Anaemia is divided into many types, depending on its causes and effects, for example: microcytic anaemia, macrocytic anaemia, aplastic

anaemia, haemolytic anaemia, polycythaemia, etc. The different types are described below in detail.

Microcytic Anaemia

In this type, RBCs are smaller in size than normal cells. Microcytic anaemia is further subdivided into four types:

The first type, known as 'iron deficiency anaemia', is due to a deficiency of iron in the blood, as the term indicates.²

The second type, called sideroblastic anaemia, is due to the inability of protoporphyrin IX to bind with iron, and also due to the accumulation of haemosiderin in the liver.³ Accumulation of haemosiderin in the liver may result in liver damage.

The third type, known as thalassaemia, is a genetic disorder characterized by the deficiency or absence of alpha or beta globin chains.⁴ There are two types of thalassaemia: one is alpha thalassaemia and the other is beta thalassaemia. Four genes control the synthesis of alpha globin chains. These genes are present on chromosome 16. If these four genes are absent, alpha globin chains are also absent, which results in hydrops fetalis. In beta thalassaemia, abnormal beta globin chains are formed due to a point mutation on chromosome 11.

The fourth type is blood loss anaemia or haemorrhage. At the first stage of haemorrhage, the loss of blood is recoverable. After 3 - 4 days of first stage haemorrhage, the blood volume may be maintained by blood transfusion; after 3 - 6 weeks, RBCs will be synthesized to their normal value, if second stage haemorrhage does not occur. The second stage of haemorrhage is actually blood loss anaemia, and is a non-recoverable stage. In this stage, the RBCs become smaller in size.

Macrocytic Anaemia

In this type of anaemia, the RBCs are larger in size than normal, due to certain factors. Based on these factors, macrocytic anaemia is further divided into three types: The first type is known as 'vitamin B₁₂ megaloblastic anaemia', and is due to a vitamin B₁₂ deficiency, as the term indicates.⁵ Due to this deficiency, reticulocytes are not converted into normal, mature RBCs.⁶ 'Megaloblastic anaemia', which is due to folic acid deficiency, is another type of anaemia. The third type is known as 'pernicious anaemia', and is also due to a vitamin B₁₂ deficiency.⁷ This happens due to so-called intrinsic factors, which are proteinic in nature and are secreted from the parietal cells of the stomach. These intrinsic

factors help in the absorption of vitamin B₁₂ from the gastrointestinal tract into the blood.

Aplastic Anaemia

Aplastic anaemia occurs due to the loss of bone marrow function. Bone marrow is mainly affected by gamma rays, chemicals like benzene, and some drugs like chloramphenicol.⁸ X-rays also affect the bone marrow. In fact, these chemical rays cause certain mutations in the bone marrow structure, which ultimately lead to the loss of bone marrow function.

Haemolytic Anaemia

Haemolytic anaemia is due to the destruction of RBCs (haemolysis). It is actually a hereditary or genetic disorder and also divided into different types:

In hereditary spherocytosis (due to mutation in spectrin), the RBCs become spherical in shape instead of biconcave.⁹ Spectrin is a protein which maintains the RBCs' membrane¹⁰ but due to the spectrin deficiency, the RBCs become spherical.

In hereditary elliptocytosis (due to mutation in the actin gene) the RBCs become elliptical in shape.¹¹ It is due to the deficiency of the protein actin.

Sickle cell anaemia is a disease in which the RBCs become sickle-shaped. Further, there is a mutation in the gene for the beta globin chain which causes a change in the amino acid sequence by replacing glutamic acid with valine.

Erythroblastosis fetalis is a disease which occurs when the Rh factors of the mother and the fetus are opposed (i.e. positive and negative). Antibodies against the fetus pass from the mother into the fetus and destroy its RBCs.¹²

Polycythaemia

Polycythaemia is characterized by an increase in RBC production. It is divided into two types: one is the secondary or physiological polycythaemia, which does not involve any pathophysiology. It is only due to living in low oxygen conditions such as high altitudes (13000-17000 feet) where there is less oxygen, that RBC production increases (6 - 7 million/mm³). Polycythaemia vera (pathological polycythaemia), is due

to certain genetic diseases, or cancer.¹³ In this case, the RBC count is 7 - 8 million/mm³.

Management of Anaemia

As we know that there are many types of anaemias, and these further have many subtypes, different types of anaemia are managed appropriately according to their individual causes or deficiencies.¹⁴

Management of microcytic anaemia

Iron deficiency anaemia can be cured by following a diet containing iron and also by taking iron-containing medications. In the case of sideroblastic anaemia, the accumulation of hemosiderin should be prevented and there is a proper way to excrete it from the body. Thalassaemia is a genetic disorder. Its treatment consists of blood transfusion or bone marrow transplantation.

Management of macrocytic anaemia

A patient suffering from macrocytic anaemia should include vitamin B₁₂ and folic acid in his/her diet, or take medicines containing them.

Management of aplastic anaemia

A loss of bone marrow function is due to radiation exposure. Consequently, one should be careful when exposed to several radiations. Also, one should avoid taking carcinogenic substances such as benzene.

Management of haemolytic anaemia

Haemolytic anaemia is a genetic disorder caused by mutations. It can be cured by gene therapy. In gene therapy, the defected part of the gene is removed or replaced by a healthy gene.

Management of polycythaemia

In this type, RBCs are produced at above the average rate. This may be a genetic disease or may be due to cancer. It can be cured by using preventative measures.

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CHAPTER FOUR

THALASSAEMIA

MUHAMMAD IMRAN QADIR AND ASMA NOOR

Summary

Thalassaemia is a genetic disorder. The symptoms of the disease will depend on its type. Those who have the thalassaemia trait or are carriers have no symptoms, so there is no need for treatment. It has been established that all forms of thalassaemia are genetic in nature. Patients with thalassaemia major or Cooley's anaemia need blood transfusions. Patients with severe thalassaemia have a serious illness. Their treatments include iron chelation, regular blood transfusion or bone marrow transplant.

Keywords: Thalassaemia, Iron chelation therapy, Deferoxamine

Introduction

Thalassaemia is a genetic disorder which results in chronic anaemia.¹ The main symptom of this disease is a decrease in the blood's volume or in haemoglobin, or oversized red blood cells. Haemoglobin present in the red blood cells has the function of carrying oxygen to different parts of the body; therefore, a decreased haemoglobin level results in a decreased supply of oxygen to the tissues.

Aetiology

Haemoglobin is composed of four globin chains; two α chains and two β chains. In thalassaemia, there is either no production, or a reduced production of globin chains. A person who has a defected gene from one parent and normal genes from the other parent is a carrier. Carriers do not have any symptoms of the disease, but have the ability to pass their

defective genes on to their offspring.² This can result in either mild or severe anaemia.

Types

The two main types of thalassaemia are:

1. *Alpha Thalassaemia*: It is caused due to the absence of the genes that encode the synthesis of the alpha chain of haemoglobin.³ The chronic form of anaemia is caused by more than two affected genes. Alpha thalassaemia major is the most chronic type of anaemia and results in miscarriage.⁴

2. *Beta Thalassaemia*: The cause of beta thalassaemia is the absence of one or both genes which are necessary for the synthesis of the beta globin chain.⁵ The types of disease depend on the type of abnormality, or whether one gene is missing or both. Chronic anaemia is caused by the absence of both genes. The chronic form of this disease is known as 'Cooley's anaemia'.⁶

Signs and Symptoms

The signs of thalassaemia depend on the type of thalassaemia. Signs of thalassaemia appear when an insufficient amount of oxygen is provided to all parts of the body due to the small quantity of haemoglobin or red blood cells.⁷ Major symptoms of thalassaemia include fatigue, yellowing of the skin or jaundice, a protruding abdomen, enlargement of the spleen and liver, dark urine, abnormal growth and abnormal facial bones.

Treatments

Treatment of this disease depends upon the severity and type of disease. Patients having the thalassaemia trait or carriers of thalassaemia do not need treatment. Patients with thalassaemia major or Cooley's anaemia need blood transfusions. Treatments for full-blown thalassaemia are: iron chelation, regular blood transfusions, or bone marrow transplantations. People with severe anaemia can live up to their 30s.⁸

Blood Transfusion

The treatment for mild or severe anaemia is the transfusion of red blood cells. This treatment provides normal blood cells with normal

haemoglobin. This process takes one to 4 hours. The normal lifespan of red blood cells is about 120 days therefore, to maintain the supply of normal blood cells, repeated transfusions are required.⁹

Folic Acid Supplements

Folic acid and vitamin B are required to produce normal blood cells.⁹ In addition to treatment with blood transfusions or iron chelation therapy, folic acid and vitamin B supplements are required.

Stem Cell Transplantation

This kind of technique or treatment replaces defective bone marrow stem cells with healthy donor cells.

Iron Chelation Therapy

Regular blood transfusions lead to an increased level of iron in the blood, as the blood contains haemoglobin which is an iron-rich protein.¹⁰

To remove the excessive quantity of iron from the body and to prevent the damage caused by this iron, iron chelation therapy is needed. Two types of drugs are used in iron chelation therapy.

1) *Deferoxamine*. This is a medicine in aqueous form given below the skin by a pump used overnight. This treatment can be slightly painful and takes time. Its side effects are problems with hearing and vision.

2) *Deferasirox*. This is a pill taken once a day. Its side effects are headaches, abdominal discomfort, diarrhea, joint pain and tiredness.

Prevention

Thalassaemia has no preventative measures. To avoid passing this disorder on to their offspring, those with thalassaemia genes can get genetic counseling, so that transmission of infected genes can be prevented. Genetic counseling involves family planning: convincing the prospective parents not to have children, thus eliminating the risk of passing on the disorder to their offspring.

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CHAPTER FIVE

ANOREXIA

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Summary

Anorexia is a term used to describe a loss of appetite. However, in terms of a disorder, anorexia can be more precisely described as a lack of appetite in the presence of the physiological need for food, characterized by a severe psychological disturbance. Short-term anorexia rarely jeopardizes the patient's health, but chronic anorexia can lead to life-threatening malnutrition. Different diseases that may lead to anorexia include AIDS, hepatitis, cirrhosis and so on.

Keywords: Special consideration, Psychological disturbance, Radiation therapy, Acquired immunodeficiency syndrome

Introduction

Lack of appetite in the presence of the physiological need for food which is characterized by a severe psychological disturbance is called anorexia.^{1, 2} Temporary anorexia seldom jeopardizes health, but persistent anorexia can lead to life-threatening malnutrition.³

Causes

Drug induced anorexia results from the use of a chemotherapeutic agent or an antibiotic.⁴ It is also an indication of digitalis-toxicity. Radiation treatment can cause anorexia as a result of biochemical changes inside the body.⁵ Nutritional maintenance of sugar levels by IV treatment may induce anorexia.^{6, 7}

Taking down the history, and performing a physical examination of the patient may reveal the reason for the disease. Physicians should:

- Note the weight of the patient.⁸ Find out the previous weight; the maximum and minimum weight. The patient's eating habits should be noted. The patient may not like the taste of a food and may refuse to eat it.⁹
- Inquire about any dental problems affecting chewing.
- Inquire if he/she has difficulties or soreness when swallowing.¹⁰
- If the medical history does not reveal an organic condition, emotional factors should be investigated. Inquiries should be made of the patient; whether if he/she knows the reason for his/her decreased appetite. Over-thinking conditions, such as the death of a relative or any problems at school or at work, can lead to sadness, and subsequently to a lack of desire for food.

Various diseases may lead to anorexia, which may include the following:

AIDS: A major characteristic is a weight loss of 7-10kg, with other symptoms including exhaustion, daylight fever, night sweats, diarrhea, cholera, haemorrhage, mouth bleeding and skin problems.

Hepatitis: In viral hepatitis (A, B, C, D), anorexia starts with fatigue, headache, mild fever and hepatomegaly.¹¹ Anorexia may start with an infection involving mild weight loss, dark urine, inflammation of the liver, and pain in the upper right side of the legs.^{12, 13}

Cirrhosis: Anorexia is also an indication of *cirrhosis*.

Symptoms

Generalized swelling, dark spots on the cheeks and under the eyes, a dull appearance, a dry and either pale or red face, missing teeth, visible cavities or dark spots on the teeth, frequently bleeding gums, enlarged thyroid glands, dry, inflamed and dark skin with lighter or darker spots, a heart rate of above 100 beats per minute, elevated blood pressure, enlarged liver and spleen, decreased libido, confusion, prosthesis in hands and feet and decreased ankle and knee reflexes are the symptoms of anorexia.^{14, 15}

Anorexia generally starts at a young age. Treatment at the start of the condition can be very useful. If not cured in time, anorexia can become a