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Introduction to hereditary angioedema

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ABSTRACT

This article discusses a rare genetic disorder that exists today and how it is managed. This article mainly discusses the research on hereditary angioedema from five aspects, including preliminary introduction, pathophysiology, treatment methods and prevention methods for analysis and research. This article will introduce the latest research data, new discoveries and treatment methods on hereditary angioedema, analyze and describe the data, and provide relevant data to illustrate the modern understanding and current situation of this disease.

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant genetic disorder that causes recurring severe swelling in parts of the body. Swelling usually occurs in the arms, legs, face, intestines, and respiratory tract. Without prior treatment, attacks usually occur every two weeks and last for several days. The estimated number of confirmed cases of HAE worldwide ranges from 15,000 to 75,000 (Sandra C. Christiansen, Joyce Wilmot,

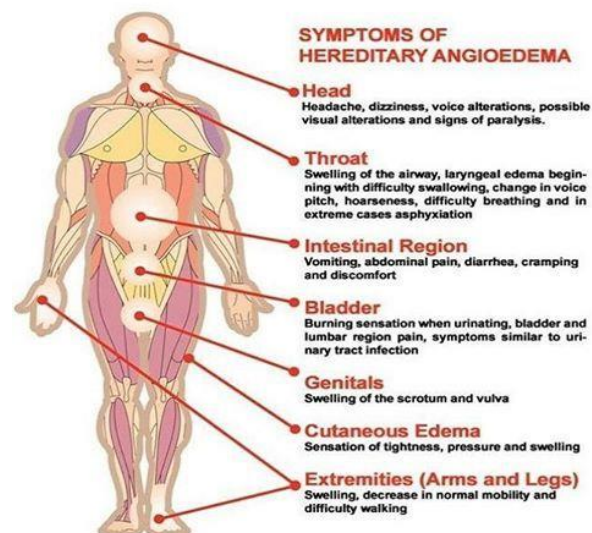
Anthony J. Castaldo, Bruce L. Zuraw, 2013). The number of confirmed cases in Taiwan is approximately 36 (Xu Shida, 2018)

HAE is divided into three main types: Type I, II, and III. HAE type I: Insufficient levels of C1 arrestin. HAE type II: Abnormal function of C1 arrestin but normal levels. HAE type III: associated with F12 gene mutations. Activation of the kinin system produces high levels of bradykinin and causes swelling. (Ali Abdulkarim, Timothy J. Craig, 2023)

Signs and symptoms

Symptoms of HAE include recurring swelling in delicate and sensitive areas such as the arms, feet, genitals, face, throat, or gastrointestinal tract. Some people will have symptoms before the attack, including itching, fatigue, weakness, and rash. Severe symptoms usually occur if it occurs in the respiratory and gastrointestinal systems. Occurs in the respiratory system and causes blockage due to tissue swelling such as difficulty breathing or airway obstruction. Digestive complications can include vomiting, abdominal pain, diarrhea and even dehydration. (Jean-Baptiste, M., Itzler, R., Prusty, S., Supina, D., & Martin, M. L, 2022)

Figure 1
The symptoms of HAE



There are three main reasons why swelling usually occurs in the arms, legs, face, intestines and respiratory tract: dense blood vessel distribution, fragile intestinal and respiratory tract mucosa, and the impact of physical activity (U.S. National Library of Medicine, 2023). HAE is edema caused by leakage of fluid (tissue fluid) from blood vessels. Areas such as arms, legs, and face have dense blood vessels and are easily affected by gravity and are also affected by abnormalities in the complement system.

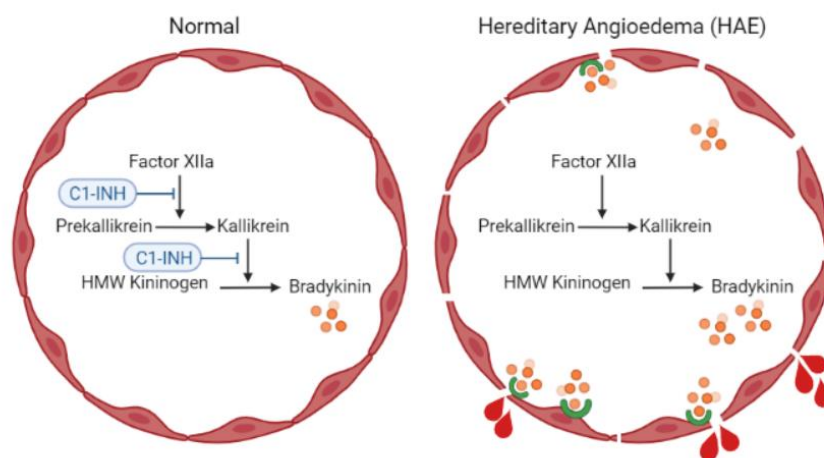
When blood vessel permeability increases, the fluid becomes more Easily leaks from inside blood vessels into tissues. Daily activities or minor irritations, such as pressure or friction, may also trigger HAE symptoms in these areas. The capillaries in these areas of the intestines and respiratory tract are also prone to edema, but the conditions are slightly different. These areas are rich in mucosa. Compared with the epithelial tissue, the mucosal tissue is more fragile and sensitive to surrounding changes. Therefore, when the complement system does not function properly, these areas are relatively prone to edema. Intestinal edema can cause severe abdominal pain, vomiting and other symptoms (Jean-Baptiste, M., Itzler, R., Prusty, S., Supina, D., & Martin, M. L, 2022), while respiratory edema may cause Difficulty breathing, or even suffocation, is particularly dangerous. If the above signs occur, it is necessary to rush to the hospital for diagnosis and examination to avoid missing the golden opportunity for treatment.

Types

HAE is divided into three types. Type I is caused by a deficiency of a complement inhibitor (C1-INH) and accounts for 85% of HAE cases with C1 inhibitor deficiency. . Type II HAE is loss of C1-INH function and accounts for approximately 15% of HAE cases. Type III HAE is associated with mutations in the F12 gene. (Ali Abdulkarim, Timothy J. Craig, 2023)

Figure 2

The mechanism of HAE



C1-INH is a plasma protein and an inhibitor of various serine proteases (Honda, D., Ohsawa, I., Mano, S., Rinno, H., Tomino, Y., & Suzuki, Y., 2021). All three types of HAE are associated with overactivation of the kinin system, resulting in the production of high levels of bradykinin. The measurement value of C1-INH can also help professional doctors determine the type and cause of HAC. Patients with type 1 HAE have significantly lower levels of C1-INH in their blood. This is because mutations in the SERPING1 gene lead to insufficient C1-INH synthesis in the body, thus leading to the occurrence of HAE. Patients with type 2 HAE do not have significantly low levels of C1-INH in their blood, but they still develop symptoms of HAE. This is because the SERPING1 gene mutation causes problems in the mechanism of synthesizing functional C1-INH in the body, resulting in a sufficient amount of C1-INH but less functional C1-INH than expected. The C1-INH in the blood of patients with type III HAE is not significantly low, but they also develop symptoms of HAE. This is because the F12 gene mutation increases the activity of coagulation factor XII, the permeability of blood vessels increases, and tissue fluid is more likely to seep from blood vessels into surrounding tissues, thereby causing edema. Therefore, the measured value of C1-INH in the blood of patients with type III HAE will not be particularly low, and the functionality of C1-INH will not be affected too much. It is mainly related to the vascular permeability caused by coagulation factors XII and HMWK. increase related.

The SERPING1 gene is mainly responsible for encoding C1-INH. C1-INH inhibits the complement system and kinin system to avoid excessive production of bradykinin (T. Gößwein, A. Kocot, G. Emmert, W. Kreuz, I. Martinez-Saguer, E. Aygören-Pürsün, E. Rusicke, K. Bork, J. Oldenburg, C.R. Müller, 2008). Excessive inflammation and excessive vascular permeability can be prevented by limiting C1 esterase, thrombin, and plasma kallikrein. When the SERPING1 gene is mutated, the quantity or functionality of C1-INH protein is reduced, leading to overactivation of the complement and kinin systems, causing tissue edema and HAE.

The main function of the F12 gene mentioned in type III HAE is to encode coagulation factor XII (Hagemann factor) (Bork, K., Wulff, K., Witzke, G., & Hardt, J., 2015).

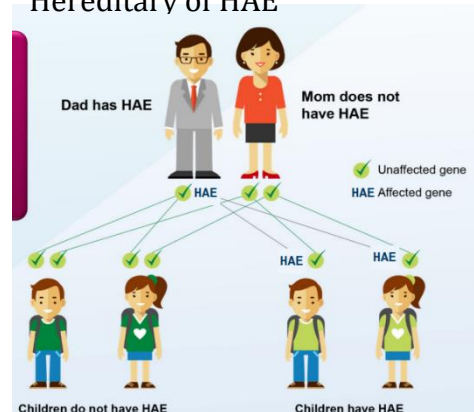
Hageman factor is involved in blood coagulation and inflammatory responses after exposure to CAS and kinin systems. When the F12 gene is mutated, the kinin system may overreact, resulting in a large increase in bradykinin, thereby increasing vascular permeability, causing tissue edema, and even triggering HAC.

Pathophysiology

Somatically dominant inheritance of HAE requires only one copy of the mutated C1 inhibitor gene to develop the disease. C1 inhibitor defects are mostly caused by mutations in the SERPING1 gene. About 700 different mutations have been discovered. Mutations in the SERPING1 gene have a certain correlation with both parents (Zuraw, B. L., & Christiansen, S. C., 2016), mainly because HAE is a somatic

chromosomal dominant genetic disease. It is therefore not uncommon to observe that both parents of patients with HAE and C1 inhibitor deficiency are unaffected. Children may still develop genetic HAE or C1 inhibitor deficiency even if their parents do not express the trait. For SERPING1 gene mutations that occur in type 1 and type 2 HAE, 75% of cases are due to chromosomal dominant inheritance of the mutated gene, and 25% of cases are due to somatic chromosomal dominant inheritance of the mutated gene.

Figure 3
Hereditary of HAE



Most cases of HAE are caused by a deficiency or dysfunction of C1 inhibitor. C1 inhibitor is responsible for regulating the complement system and cryocoagulase system. When its function is insufficient, it will cause increased vascular permeability and cause edema in specific parts. It is also an inhibitor of the plasma contact system. However, in type 1 and 2 HAE, the quantity and function of C1 inhibitors are reduced (type 1) or dysfunctional (type 2), resulting in bradykinin deinhibition and endothelial cadherin phosphorylation, internalization and Degradation (Zuraw, B.L., Christiansen, S.C., 2016). Phosphorylation of cadherin mainly refers to the activation of the bradykinin system caused by the lack of C1 inhibitor, which causes cadherin to be modified and degraded by

phosphate groups in cells, affecting cell adhesion and cytoskeletal structure, causing the actin cytoskeleton to shrink. , the pore size of vascular endothelial cells increases, and vascular endothelial growth factor (VEGF) is activated. Therefore, the barrier between these endothelial cells weakens, resulting in increased vascular permeability, and the interstitial fluid in the blood vessels penetrates into the surrounding tissue, causing edema and the occurrence of HAE. Characteristic swelling seen.

HAE with normal C1-INH values is a genetically heterogeneous disease (Woodward, A. A., Urbanowicz, R. J., Naj, A. C., & Moore, J. H., 2022). Mainly can be divided into two types. They are allelic heterogeneity and genetic heterogeneity.

Allelic heterogeneity is common in genetic diseases and usually refers to different genetic mutations of the same gene leading to similar disease manifestations. Although these mutations occur in the same genome, they may affect gene expression or have different functions of the proteins translated by the genes due to point mutations, deletions or insertions, leading to different disease manifestations.

Genetic heterogeneity means that mutations in different genes can cause similar disease manifestations. But compared with genetic heterogeneity, it depends on whether the mutation occurs in the same gene. Gene heterogeneity can be divided into two types: site heterogeneity and expression heterogeneity. Locus heterogeneity refers to the fact that mutations at different genetic loci lead to similar symptoms. Hereditary angioedema (HAE) mentioned in this article can be caused by mutations in different genes such as the SERPING1 gene and the F12 gene. Phenotypic heterogeneity refers to the same genetic mutation causing different clinical manifestations or disease severity in different individuals. One person may experience mild symptoms due to the same genetic defect, while another may face severe health problems.

HAE has discovered some molecular subtypes through genetic research. The first subtype was identified to be caused by mutations in the F12 gene encoding coagulation factor XII (Dewald G, Bork K, 2006). All four mutations known so far affect the accelerated

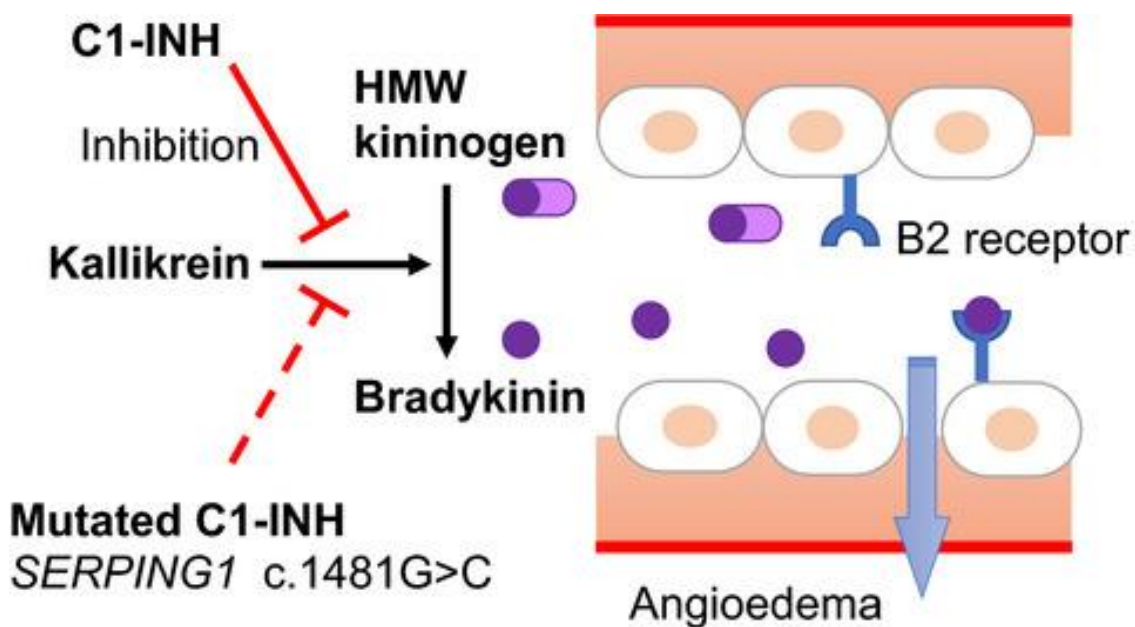
activation of coagulation factor XII and the kallikrein-kinin system. In particular, the fourth subtype is similar to the third type but primarily affects women. (Jones D, Zafra H, Anderson J, 2023) Although the clinical manifestations of HAE caused by F12 gene mutations have a greater impact on women, they are not limited to female mutation carriers who will develop HAE. F12 gene mutations cause significant estrogen sensitivity and produce the symptoms of HAE. Although men inherit the mutated gene, they may be asymptomatic carriers. The second molecular subtype of HAE with normal C1 inhibitors belongs to another form of type III HAE. The second molecular subtype is caused by mutations in the plasminogen kringle 3 gene, resulting in a novel form of dysplasminogenemia. Mutated plasminogen is a kininogenase that directly causes bradykinin release from kininogen.

Medical therapy

In modern treatment methods, stimulating the synthesis of C1 inhibitors or reducing the consumption of C1 inhibitors is the main treatment method. Medication is the main form of treatment.

Figure 4

The mechanism of inhibitors working in cells



Icatibant (Cicardi, M., Banerji, A., Bracho, F., Malbrán, A., Rosenkranz, B., Riedl, M., Bork, K., Lumry, W., Aberer, W., Bier, H., Bas, M., Greve, J., Hoffmann, T. K., Farkas, H., Reshef, A., Ritchie, B., Yang, W., Grabbe, J., Kivity, S., Kreuz, W., ... Fan, W. T., 2010) is a bradykinin B2 receptor antagonist. The symptoms of HAE are mainly caused by an increase in the concentration of bradykinin in the blood. Bradykinin binds to B2 receptors on vascular endothelial cells, causing vasodilation and increased permeability, causing significant edema. The mechanism of action of ecarantide is to prevent the binding of bradykinin to B2 receptors, thereby reducing the permeability of the vascular endothelium. When bradykinin overactivates B2 receptors, patients are prone to swelling, pain, and even difficulty breathing. Ecallantide is given as a subcutaneous injection and reaches its maximum effect within 30 minutes to two hours.

Ecallantide (Lawrence M. Lewis, Charles Graffeo, Pascal Crosley, Howard A. Klausner, Carol L. Clark, Anthony Frank, James Miner, Ryan Iarrobino, Yung Chyung, 2015) is a selective kallikrein inhibitor. The mechanism of action is to reduce vascular permeability by inhibiting the activity of kinins. It is usually administered as a subcutaneous injection and used during the onset of HAE symptoms to quickly relieve swelling and discomfort. This drug has been clinically proven effective and is widely used.

Lanadelumab (Takhzyro) (Banerji A, Riedl MA, Bernstein JA, et al., 2018) is a human monoclonal antibody that is usually injected subcutaneously every two or four weeks. The mechanism of action is the inhibition of kallikrein (plasma kallikrein). Lanadelumab reduces the occurrence of swelling and inflammation by inhibiting the activity of kallikrein and reducing bradykinin levels. In February 2023, the FDA approved expanded use of lanadelumab (Takhzyro) to prevent the onset of hereditary angioedema in children aged 2 to 12 years.

Conestat alfa (Ruconest) (Farkas, H. 2016) is a C1 esterase inhibitor that typically takes effect within minutes of intravenous administration, providing rapid relief to patients with HAE. The mechanism of action is to reduce the activity of kallikrein and bradykinin by mimicking naturally occurring C1 inhibitors in the body. In October 2010, the European

Medicines Agency authorized conestat alfa (Ruconest) for the treatment of acute angioedema attacks.

Cinryze (Jonathan A. Bernstein, Michael E. Manning, Henry Li, Martha V. White, James Baker, William R. Lumry, Mark A. Davis-Lorton, Kraig W. Jacobson, Richard G. Gower, Colin Broom, David Fitts, Jennifer Schranz, 2014) is made from C1 esterase inhibitor extracted from human plasma, which can supplement the lack or dysfunction of C1 inhibitor in HAE patients. It is usually given as an intravenous injection at regular intervals every few days. The mechanism of action is to prevent excessive activation of the complement system, thereby reducing vascular permeability and reducing the risk of edema.

Sebetralstat (Riedl, M. A., Farkas, H., Aygören-Pürsün, E., Psarros, F., Soteres, D. F., Staevska, M., Cancian, M., Hagin, D., Honda, D., Melamed, I., Savic, S., Stobiecki, M., Busse, P. J., Dias de Castro, E., Agmon-Levin, N., Gower, R., Kessel, A., Kurowski, M., Lleonart, R., Grivcheva Panovska, V., ... KONFIDENT Investigators, 2024) is an oral plasma kallikrein inhibitor. It can be taken orally or by subcutaneous injection, and usually takes effect within a few hours after injection. The mechanism of action is mainly through competitive binding to the active site of kallikrein to inhibit the enzymes in the kinin system to reduce the production of bradykinin. When bradykinin levels are reduced, vascular permeability and edema can be effectively reduced. This drug selectively binds to prekallikrein messenger RNA (mRNA) and degrades it via ribonuclease H1, resulting in reduced production of prekallikrein protein.

Berotalstat (Lee A., 2021) is an oral drug that has certain effectiveness in preventing hereditary angioedema (HAE). The mechanism of action is to reduce the production of bradykinin in blood vessels that promotes swelling by inhibiting the activity of kininase. Berotalstat was approved in the United States in December 2020 to prevent attacks of hereditary angioedema in people 12 years and older.

The use of androgens (danazol, stanazol, and mestrol) is one way to treat hereditary angioedema (HAE) (Guo, Y., Zhang, H., Lai, H., Wang, H. , Chong-Neto, H. J., Valle, S. O. R., & Zhu, R., 2022), the mechanism of androgens in the body is mainly based on the drug's effect on C1-INH gene expression. This class of drugs is mainly used to enhance the synthesis of C1-INH and reduce excessive activation of the complement system. The androgen complex increases the production of C1-INH protein by promoting the synthesis of mRNA, thereby supplementing the concentration of C1-INH in the patient's body. This type of regulation, after increasing C1-INH levels, can reduce the increase in vascular permeability and body fluid leakage caused by the activation of the complement system, thus reducing the frequency and severity of edema attacks. However, these drugs may cause virilization, abnormal liver function, abnormal blood lipids, weight gain, and irregular menstruation in female patients.

Long term, pdC1INH is an option. pdC1INH is a C1 inhibitor recombinantly produced from human cells (Malbrán, A., Malbrán, E., Menéndez, A., & Fernández Romero, D. S., 2014), which can replace the C1 inhibitor lacking in patients and can regulate the complement system and reduces vascular permeability by inhibiting enzymes associated with inflammation and edema. Subcutaneous injections given in the early stages of an attack can quickly reduce the degree of edema and improve symptoms, with symptom relief felt within hours of administration.

Genetical therapy

Gene therapy (Longhurst HJ, Lindsay K, Petersen RS, Fijen LM, Gurugama P, Maag D, et al., 2024) Research on HAE mainly focuses on C1-INH deficiency caused by mutations in the SERPING1 gene. Through precise gene editing technology, the mutation of the SERPING1 gene is corrected and the expression of C1-INH is restored to normal. An important strategy for such a treatment is to insert the normal-function SERPING1 gene into patient cells based on CRISPR/Cas9 technology, allowing it to produce enough C1-INH protein to reduce edema caused by excessive activation of the complement system. There is also a potential one-time gene editing therapy, NTLA-2002, which targets the (KLKB1) gene to prevent HAE attacks. In addition to CRISPR/Cas9, gene

therapy can also use viral vectors to deliver corrected genes to target cells, thereby alleviating HAE symptoms in the long term. The experimental gene therapy BMN 331 also prevents the disease by targeting the SERPING1 gene with an adeno-associated virus. However, there is still room for research on the long-term stability, safety and risk of immune reactions of this type of treatment.

RNA therapy (Li H. H., 2020) is an emerging technology that treats diseases by regulating RNA. RNA therapy mainly relies on technologies such as messenger RNA (mRNA), antisense oligonucleotides (ASO) and RNA interference (RNAi). mRNA therapy delivers mRNA encoding specific proteins into cells, allowing the cells to synthesize the required proteins themselves. ASO binds to specific mRNA through short-chain RNA sequences, inhibits its translation or promotes degradation, thereby regulating the expression of SERPING1 or F12 genes. RNAi therapy uses double-stranded RNA to trigger intracellular mechanisms to reduce the production of specific proteins. In hereditary angioedema (HAE), RNA therapy can target the F12 or SERPING1 gene mutations that cause HAE, reducing overactivation of the complement system and thus alleviating symptoms. But the stability of RNA therapy still needs to be increased.

Conclusion

This paper mainly discusses the clinical manifestations, pathophysiological mechanisms, diagnosis and treatment methods of the rare genetic disease "Hereditary Angioedema (HAE)". HAE is a somatic chromosomal dominant genetic disease that causes repeated edema in patients' hands, feet, face, digestive system, respiratory tract and other parts of the body, and can easily lead to serious complications. According to different causes of disease, HAE is divided into three types: type I, type II and type III. Each type has different pathogenic mechanisms. The cause of edema in this disease is mainly abnormal activation of the complement and kinin systems, which increases vascular permeability, leading to extravasation of tissue fluid into surrounding tissues.

In terms of treatment, there are currently a variety of therapies that can control or prevent HAE attacks, mainly targeting the inhibition of kinins and the complement system.

Common subcutaneous injection drugs include ecallantide, icarantide, lanadelumab, etc., which reduce vascular permeability by preventing kinin receptor binding or inhibiting kallikrein. There are also some oral drugs, such as Sebetralstat and Berotralstat, which have also shown good results. In addition, androgens can increase the expression of C1-INH to reduce attacks. C1-INH supplements are also used for long-term treatment and can effectively replenish C1-INH in patients and relieve edema symptoms.

In summary, through in-depth understanding of the pathogenic mechanism of HAE and research on various drugs, modern medicine can effectively control and reduce the frequency and severity of this disease. With the continuous efforts of many scientists, such rare diseases are not unsolvable, but there are still many opportunities for patients to return to normal daily life to a certain extent. With the advancement of modern science and technology, in addition to general drug treatment, there is also the ongoing development of gene therapy. Although this technology still has a lot of room for improvement, in the future, it may no longer be impossible to cure this type of disease.

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