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Behcet’s Disease

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1. WHAT IS BEHCET’S DISEASE

1.1 What is it?

Behçet’s syndrome, or Behçet’s disease (BD), is a chronic inflammatory condition of unknown cause that leads to inflammation of blood vessels throughout the body (systemic vasculitis). The mucosa (tissue that produces mucous, which is found in the lining of the digestive, genital and urinary organs) and skin are affected and the main symptoms are recurrent oral and genital ulcers and eye, joint, skin, blood vessel and nervous system involvement. BD was named after a Turkish doctor, Prof. Dr. Hulusi Behçet, who described it in 1937.

1.2 How common is it?

BD is more common in some parts of the world, especially along the historical ‘silk route’, including the Far East (such as Japan, Korea, and China), Middle East (Iran) and Mediterranean basin (Turkey, Tunisia, Morocco). The prevalence rate (number of patients in the population) in the adult population is 100-300 cases/100,000 people in Turkey, 1/10,000 in Japan, and 0.3/100,000 in Northern Europe. According to a study conducted in 2007, the prevalence of BD in Iran is 68/100,000 inhabitants (2nd highest in the world after Turkey). Few cases are reported from the United States and Australia.
BD in children is rare, even in high risk populations. The diagnostic criteria are fulfilled before the age of 18 in approximately 3-8% of all BD patients. Overall, the age of disease onset is 20-35 years. Girls and boys are equally affected but in some countries boys may be more severely affected.

1.3 What are the causes of the disease?

The causes of the disease are unknown. Recent research carried out in a large number of patients suggests that genetic susceptibility may have some role in the development of BD. There is no known specific trigger. Research into the cause and treatment is being carried out in several centres.

1.4 Is it inherited?

There is no consistent pattern of inheritance of BD, although some genetic susceptibility is suspected, especially in early onset cases. The syndrome is associated with a genetic predisposition (HLA-B5), especially in patients originating from the Mediterranean basin and the Far East. There have been reports of families suffering from this disease.

1.5 Why does my child have this disease? Can it be prevented?

BD cannot be prevented and its cause is unknown. There is nothing that you could have done to prevent your child from getting BD. It is not your fault.

1.6 Is it infectious?

No, it is not.

1.7 What are the main symptoms?

Mouth ulcers: These lesions are almost always present and they are the first sign of the disease in about two-thirds of patients. The majority of children develop multiple, minor ulcers, indistinguishable from recurrent ulcers, which are common in childhood. Large ulcers are rarer and may be very difficult to treat.

Genital ulcers: In boys, the ulcers are located mainly on the scrotum and, less frequently, on the penis. In adult male patients, these almost always leave a scar. In girls, external genitalia are mainly affected. These ulcers resemble the oral ulcers. Children have fewer genital

ulcers before puberty. Boys may have recurrent orchitis (testicular inflammation).

Skin involvement: There are different skin lesions. Acne-like lesions are present only after puberty. Erythema nodosum are red, painful, nodular lesions, usually located on the lower legs. These lesions are more frequent among children before puberty.

Pathergy reaction: Pathergy is the reactivity of the skin of BD patients to a needle prick. This reaction is used as a diagnostic test in BD. After a skin puncture with a sterile needle on the forearm, a papule (raised round circular rash) or pustule (round raised pus-containing rash) forms within 24 to 48 hours.

Eye involvement: This is one of the most serious symptoms of the disease. While the overall prevalence is approximately 50%, it increases to 70% in boys. Girls are less frequently affected. The disease involves both eyes in most patients. Eyes are involved usually within the first three years after the disease onset. The course of the eye disease is chronic, with occasional flares. Some structural damage occurs as a result of each flare, causing gradual vision loss. Treatment is focused on controlling the inflammation, preventing the flares and avoiding or minimizing vision loss.

Joint involvement: Joints are involved in about 30-50% of children with BD. Usually ankles, knees, wrists and elbows are affected, and typically fewer than four joints are involved. The inflammation can cause joint swelling, pain, stiffness and restriction of movement. Fortunately, these effects usually last only a few weeks and resolves on their own. It is very rare for this inflammation to cause joint damage.

Nervous system involvement: Rarely, children with BD can develop problems with their nervous system. This may cause seizures, headaches and cerebral symptoms, increased intracranial pressure (pressure inside the skull), or problems with balance or movement. The most severe forms are seen in males. Some patients may develop psychiatric problems.

Blood vessel involvement: Blood vessel involvement is seen in about 12-30% of juvenile BD patients and can signal a poor outcome. Both veins and arteries may be involved. Any vessel size in the body can be involved; hence the classification of the disease as "variable vessel size vasculitis". The vessels of the calves are commonly affected, becoming swollen and painful.

Gastrointestinal involvement: This is especially common in

patients from the Far East. Examination of the bowel reveals ulcers.

1.8 Is the disease the same in every child?

No, it is not. Some children may have mild disease with infrequent episodes of oral ulcers and some skin lesions, while others may develop eye or nervous system involvement. There are also some differences between girls and boys. Boys usually experience a more severe disease course, with more eye and blood vessel involvement, than girls. Besides the different rates of people affected in different countries, how children are affected may also differ throughout the world.

1.9 Is the disease in children different from the disease in adults?

BD is rare in children compared to adults, but there are more familial cases among children with BD than in adults. The disease manifestations after puberty are more similar to the disease in adults. More generally, in spite of some variations, BD in children does resemble the adult disease.

2. DIAGNOSIS AND THERAPY

2.1 How is it diagnosed?

The diagnosis is primarily clinical (based on a collection of symptoms and signs). It may take one to five years before a child fulfils the international criteria described for BD. These criteria require the presence of oral ulcers plus 2 of the following characteristics: genital ulcers, typical skin lesions, a positive pathergy test or eye involvement. The diagnosis is usually delayed for an average of three years.
There are no specific laboratory findings for BD. Approximately half of children with BD carry the genetic marker HLA-B5 and this is linked to the more severe forms of the disease.
As described above, a pathergy skin test is positive in about 60-70% of patients. However, the frequency is lower in some ethnic groups. To diagnose vascular and nervous system involvement, specific imaging of the vessels and the brain may be needed.
As BD is a multi-system disease (it can affect many parts of the body), specialists in the treatment of eyes (ophthalmologist), skin

(dermatologist) and the nervous system (neurologist) co-operate in treatment.

2.2 What is the importance of tests?

A pathergy skin test may help in diagnosis. It is included in the International Study Group classification criteria for Behçet's Disease. Three skin punctures are applied on the inner surface of the forearm with a sterile needle. It hurts very little and the reaction (raised lump in the skin) is evaluated 24 to 48 hours later. Increased hyper-reactivity of the skin can also be seen at sites where blood is taken or after surgery. Therefore, patients with BD should not undergo unnecessary interventions.

Some blood tests are done to rule out other conditions that can mimic BD, but there is no specific laboratory test for BD. In general, tests show that inflammation is mildly elevated. Moderate anaemia and an increase in white blood cell count may be detected. These tests only need repeating when your doctor thinks this may be helpful to monitor the disease or medication side-effects.

Several imaging techniques are used in children with blood vessel and nervous system involvement.

2.3 Can it be treated or cured?

The disease can go into remission, but may have flare-ups. It can be controlled, but not cured.

2.4 What are the treatments?

There is no specific treatment, because the cause of BD is unknown. Different organ involvement requires different treatment approaches. At one end of the spectrum there are patients with BD who do not need any therapy. On the other end, patients with eye, central nervous system and blood vessel disease may require a combination of treatments. Almost all available data on the treatment of BD comes from adult studies. The main drugs are listed below:

Colchicine: This drug used to be prescribed for almost every symptom of BD, but in a recent study it was shown to be more effective in the treatment of joint problems and erythema nodosum (painful

lumps on shins) and mouth ulcers.

Corticosteroids: Corticosteroids are very effective in controlling inflammation. Corticosteroids are primarily administered to children with eye, central nervous system and blood vessel disease, usually in large doses by mouth (1-2 mg/kg/day). When needed, they can be also given intravenously (into a vein) at higher doses (30 mg/kg/day, to be administered in three doses on alternate days) to achieve an immediate response. Topical (locally administered) corticosteroids are used to treat mouth ulcers and eye disease (in the form of eye drops for the latter).

Immunosuppressive drugs: This group of drugs is administered to children with severe disease, especially for eye and major organ or blood vessel involvement. They include azathioprine, cyclosporine-A and cyclophosphamide.

Antiaggregant and anticoagulant therapy: Both options are used occasionally in children with blood vessel involvement. In the majority of patients, aspirin is probably sufficient for this purpose.

Anti-TNF therapy: This new group of drugs is useful for certain features of the disease.

Thalidomide: This drug is used at some centres to treat major mouth ulcers.

Local treatment for oral and genital ulcers is very important. The treatment and follow-up of BD patients requires a team approach. In addition to a paediatric rheumatologist, an ophthalmologist and a haematologist should be included in the team. The family and the patient should always be in touch with the physician or the centre responsible for treatment.

2.5 What are the side effects of drug therapy?

Diarrhoea is the most common side effect of colchicine. In rare cases, this drug may cause a drop in the number of white blood cells or platelets. Azospermia (a decrease in sperm counts) has been reported but is not a major problem with the therapeutic doses used for this disease; sperm counts return to normal when the dose is lowered or the treatment is stopped.

Corticosteroids are the most effective anti-inflammatory drugs, but their use is limited, because in the long-term they are associated with serious side effects, like diabetes mellitus, high blood pressure, osteoporosis

(brittle bones), cataract formation and reduced growth. Children who have to be treated with corticosteroids should receive it once a day, in the morning. For prolonged administration, calcium preparations should be added to the treatment.
Of the immunosuppressive drugs, azathioprine may be toxic to the liver, may cause a decrease in the number of blood cells and increase susceptibility to infections. Cyclosporin-A is mainly toxic to the kidneys, but it may also cause high blood pressure, or an increase in body hair and problems with the gums. The side effects of cyclophosphamide are mainly depression of bone marrow and bladder problems. Long-term administration interferes with the menstrual cycle and may cause infertility. Patients being treated with immunosuppressive drugs must be followed closely and should have blood and urine tests every one or two months.
Anti-TNF drugs and other biologic agents are also being increasingly used in children who do not respond to first line treatments. Anti-TNF and other biologics increase the frequency of infections.

2.6 How long should treatment last?

There is no standard answer to this question. Generally, immunosuppressive therapy is stopped after a minimum of two years or once the patient has been in remission for two years. However, in children with blood vessel and eye disease, where complete remission is not easy to achieve, the therapy may last much longer. In such instances, the medication and doses are modified according to new or on-going symptoms.

2.7 What about unconventional or complementary therapies?

There are many complementary and alternative therapies available and this can be confusing for patients and their families. Think carefully about the risks and benefits of trying these therapies as there is little proven benefit and they can be costly in terms of time, burden to the child and money. If you are interested in seeking complementary and alternative therapies, please discuss these options with your paediatric rheumatologist. Some therapies can interact with conventional medications. Most doctors will not be opposed to you seeking other options, provided you follow medical advice. It is very important not to

stop taking your prescribed medications. When medications are needed to keep the disease under control, it can be very dangerous to stop taking them if the disease is still active. Please discuss medication concerns with your child’s doctor.

2.8 What kind of periodic check-ups are necessary?

Periodic check-ups are necessary to monitor disease activity and treatment and are especially important for children with eye inflammation. An eye specialist experienced in treating uveitis (inflammatory eye disease) should examine the eyes. The frequency of check-ups depends on the disease activity and on the type of medication being used.

2.9 How long will the disease last?

Typically, the course of the disease includes periods of remission and episodes of flares. The overall activity generally decreases with time.

2.10 What is the long-term prognosis (predicted course and outcome) of the disease?

There is very limited data on the long-term outcome of patients with childhood BD. From the data available, we know that many patients with BD do not need any treatment. However, children with eye, nervous system and blood vessel involvement require special treatment and follow-up. BD can be fatal, but only in rare cases. This is mainly because of a consequence of blood vessel involvement (rupture of pulmonary arteries or other peripheral aneurysms - balloon like dilations of blood vessels), severe central nervous system involvement and intestinal ulcerations and perforations, seen especially among certain ethnic groups of patients (e.g. Japanese). The main cause of morbidity (poor outcome) is eye disease, which can be very severe. The child’s growth may be retarded, mainly as a secondary consequence of steroid therapy.

2.11 Is it possible to recover completely?

Children with milder disease may recover, but the majority of paediatric

patients have long periods of remission followed by flare-ups of the disease.

3. EVERYDAY LIFE

3.1 How might the disease affect the child and the family's daily life?

Like any other chronic disease, BD does affect the child and the family's daily life. If the disease is mild, with no eye or other major organ involvement, the child and family generally can lead a normal life. The most common problem is recurrent mouth ulcers, which may be troublesome for many children. These lesions may be painful and can interfere with eating and drinking. Eye involvement may also be a serious problem for the child and family.

3.2 What about school?

It is essential to continue education in children with chronic diseases. In BD, unless there is eye or other major organ involvement, children can attend school regularly. Visual impairment may require special educational programs.

3.3 What about sports?

The child can participate in sports activities as long as they exhibit only skin and mucosa involvement. During attacks of joint inflammation, sports may need to be avoided. Arthritis (joint inflammation) in BD is short-lived and resolves completely. The patient should be able to resume sports activities after the inflammation is gone. However, children with eye and blood vessel problems may need to limit their activities. Prolonged standing should be discouraged in patients with blood vessel involvement of the lower extremities.

3.4 What about diet?

There is no restriction regarding food intake. In general, children should observe a balanced, normal diet for their age. A healthy, well-balanced diet with sufficient protein, calcium and vitamins is recommended for a

growing child. Overeating should be avoided in patients taking corticosteroids because these drugs may increase appetite.

3.5 Can climate influence the course of the disease?

No, there is no known effect of climate on BD.

3.6 Can the child be vaccinated?

Immunisations should be discussed with your doctor who will help decide which vaccines your child can receive. If a patient is being treated with an immunosuppressive drug (corticosteroids, azathioprine, cyclosporine-A, cyclophosphamide, anti-TNF, etc.), vaccination with live attenuated viruses (such as anti-rubella, anti-measles, anti-parotitis, anti-polio Sabin) must be postponed.
Vaccines that do not contain living viruses (tetanus, diphtheria, inactivated polio, hepatitis B, pertussis (whooping cough), pneumococcus, haemophilus, meningococcus, influenza (flu vaccine by injection) can be administered.

3.7 What about sexual life, pregnancy and birth control?

One of the major symptoms that can affect sexual life is the development of genital ulcers. These can be recurrent and painful and can therefore interfere with sexual intercourse. Women with BD typically have a mild form of the disease and should experience a normal pregnancy. Contraception should be considered if a patient is being treated with immunosuppressive drugs. Patients are advised to consult their doctor about contraception and pregnancy.