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Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE)

Version of 2016

1. WHAT IS CANDLE

1.1 What is it?

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE) is a rare genetic disease. In the past, it has had a number of other names including: Nakajo-Nishimura syndrome or Japanese Autoinflammatory Syndrome with Lipodystrophy (JASL) or Joint contractures, muscle atrophy, microcytic anaemia, and panniculitis-induced childhood-onset lipodystrophy (JMP). Affected children suffer from recurrent episodes of fever, a rash which heals leaving bruise-like lesions, muscle wasting, progressive loss of the layer of fat under the skin (lipodystrophy), arthralgia and joint contractures. Untreated, the disease may lead to severe disability and even death.

1.2 How common is it?

CANDLE is a rare disease. Currently, almost 60 cases have been described in literature but there are likely to be more who have not yet been diagnosed.

1.3 Is it inherited?

It is inherited as an autosomal recessive disease (which means that it is not linked to gender and that neither parent needs to show symptoms of the disease). This type of transmission means that to have CANDLE,

an individual must have inherited one faulty or mutated gene from the mother and the other from the father. Hence, both parents are healthy carriers (a carrier has only one mutated copy but not the disease). Parents who have a child with CANDLE have a 25% risk that a second child will have CANDLE as well. Antenatal diagnosis is possible.

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

The child has the disease because it was born with the mutated genes that cause CANDLE.

1.5 Is it infectious?

No, it is not.

1.6 What are the main symptoms?

Disease onset is in the first 2 weeks to 6 months of life. During the paediatric age, presenting manifestations include recurrent fever and attacks of erythematous, annular cutaneous plaques that can last for a few days to a few weeks and that leave residual purpuric lesions. The eye lids can appear rather thick or swollen with a reddish purple colour and the lips can look swollen.
Peripheral lipodystrophy (mainly in the face and upper limbs) usually appears towards the end of the first year of life and gets gradually worse over time.
Arthralgia without arthritis is also noted in most patients and significant joint contractures develop over time. Less common features of the disease include red eyes, inflammation of the deep tissues of ear and nose and attacks of headache due to inflammation of the brain lining. Lipodystrophy is progressive and irreversible.

1.7 What are the possible complications?

Infants and young children with CANDLE develop progressive enlargement of the liver and loss of both fat and muscle. Other problems, such as an enlarged heart, heart rhythm problems (arrhythmia) and joint contractures may occur later in life.

1.8 Is the disease the same in every child?

All affected children are likely to be seriously ill. However, the symptoms are not the same in every child. Even within the same family, not every affected child will be equally ill.

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

The progressive course of the disease means that the clinical picture in children may be a bit different to that observed in adults. Children present mainly with recurrent episodes of fever, stunted growth, unique facial features and rash. Muscle atrophy, joint contractures and peripheral lipodystrophy usually appear later in childhood and into early adulthood. Adults may even develop dangerous alterations in heart rhythm and an enlarged and poorly functioning heart.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

First there has to be a suspicion of CANDLE based on the disease features. CANDLE can only be proven by genetic analysis. The diagnosis of CANDLE is confirmed if the patient carries 2 mutations, one from each parent. Genetic analysis may not be available in every tertiary care centre.

2.2 What is the importance of tests?

Blood tests such as erythrocyte sedimentation rate (ESR), CRP, whole blood count and fibrinogen are carried out during disease activity to evaluate the extent of inflammation and anaemia; tests of liver enzymes are performed to assess liver involvement.
These tests are periodically repeated to evaluate if the results are back to or near normal. A small amount of blood is also needed for the genetic analysis.

2.3 Can it be treated or cured?

CANDLE cannot be cured since it is a genetic disease.

2.4 What are the treatments?

There is no effective therapeutic regimen for CANDLE syndrome. High doses of steroids (1-2 mg/kg/day) have been shown to improve some symptoms including skin eruptions, fever and joint pain but once tapered, these manifestations often return. Tumour necrosis factor alpha (TNF-alpha) inhibitors have provided temporary improvement in some patients but gave rise to flares in others. The immunosuppressive drug, tocilizumab, has shown minimal efficacy. Experimental studies with the use of JAK-kinase inhibitors (tofacitinib) are ongoing.

2.5 What are the side effects of drug therapy?

Corticosteroids are associated with possible side effects such as weight gain, swelling of the face and mood swings. If the steroids are prescribed for a prolonged period, they can cause suppression of growth, osteoporosis, high blood pressure and diabetes.
TNF-α inhibitors are recent drugs; they can be associated with an increased risk of infection, activation of tuberculosis and possible development of brain or other immune diseases. A potential risk of development of malignancies has been discussed; at present, there are no statistical data proving an increased risk of malignancies with these drugs.

2.6 How long should treatment last?

Treatment is life-long.

2.7 What about unconventional or complementary therapies?

There is no evidence concerning this type of therapy for CANDLE Syndrome.

2.8 What kind of periodic check-ups are necessary?

Children should be seen regularly (at least 3 times yearly) by their paediatric rheumatologist to monitor the control of the disease and

adjust the medical treatment. Children being treated should have blood and urine tests at least twice yearly.

2.9 How long will the disease last?

CANDLE is a life-long disease. However, the activity of the disease may fluctuate over time.

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

Life expectancy can be reduced, with death often the result of multi-organ inflammation. Quality of life is often poor as patients suffer from reduced activity, fever, pain and repeated episodes of severe inflammation.

2.11 Is it possible to recover completely?

No, because it is a genetic disease.

3. EVERYDAY LIFE

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

The child and family face major problems before the disease is diagnosed.
Some children have to deal with bone deformities, which may seriously interfere with normal activities. The daily injections may be a burden, not just because of the discomfort, but also because the storage requirements of anakinra may interfere with travel.
Another problem may be the psychological burden of life-long treatment. Patient and parent education programs can address this issue.

3.2 What about school?

It is essential to continue education in children with chronic diseases. There are a few factors that may cause problems for school attendance

and it is therefore important to explain the child’s possible needs to teachers. Parents and teachers should do whatever they can to allow the child to participate in school activities in a normal way, in order not only for the child to be successful academically but also to be accepted and appreciated by both peers and adults. Future integration into normal adult life is essential for the young patient and is one of the general aims of the care of chronically ill patients.

3.3 What about sports?

Playing sports is an essential aspect of the everyday life of any child. One of the aims of therapy is to allow children to conduct a normal life as much as possible and to consider themselves not different from their peers. All activities can therefore be performed as tolerated. However, restricted physical activity or rest may be necessary during the acute phases.

3.4 What about diet?

There is no specific diet.

3.5 Can climate influence the course of the disease?

As far as we know, climate cannot influence the course of the disease.

3.6 Can the child be vaccinated?

Yes, in general the child can be vaccinated. However, parents need to contact the treating physician for the live attenuated vaccine.

3.7 What about sexual life, pregnancy, birth control?

So far, no information on this aspect in adult patients is available in the literature. As a general rule, like with other autoinflammatory diseases, it is better to plan a pregnancy in order to discuss the effects of disease and treatments on the developing baby.