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A Shedding light on Candle Syndrome: Causes, Symptoms and Treatment options

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Abstract: *The rare inherited autoinflammatory condition known as CANDLE syndrome (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature) is caused by aberrant proteasome–immunoproteasome function. distinct abnormalities in the catalytic activity of the proteasome–immunoproteasome are caused by a number of recessive mutations in distinct protein subunits of this system, which can be found in either one subunit (monogenic, homozygous, or compound heterozygous) or two subunits (digenic and compound heterozygous). The end effect is a persistent production of type 1 interferons (IFNs), which can be significantly boosted by common triggers such viral infections, stress, or cold. Patients have a distinctive and recognizable phenotype, which includes wasting, a typical fat loss, recurrent or sometimes daily fevers, and prominent skin lesions from very early infancy. Although there is currently no effective treatment for CANDLE syndrome, baricitinib, a JAK inhibitor, appears to be somewhat beneficial. All of the pathophysiological, clinical, and laboratory characteristics of CANDLE syndrome are thoroughly reviewed in this article.*

Keywords: Syndrome, Dermatosis, Lipodystropy, Interferons

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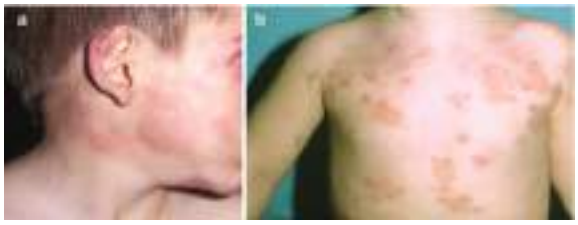
1. Introduction

The abbreviation CANDLE stands for Chronic Atypical Neutrophilic Dermatosis with Elevated Temperature and Lipodystrophy [1]. In addition to typical skin lesions, lipodystrophy, and signs of multisystem inflammation, CANDLE syndrome is an autoinflammatory disease (AID) that manifests as recurring fever in the first few months of life. CANDLE syndrome is brought on by mutations in many genes that code for protein components of the proteasome immunoproteasome pathway. Recurrent fevers, skin rashes, joint swelling, and lipodystrophy loss of body fat are its defining characteristics.



Genetic abnormalities that cause the immune system to become overactive and produce inflammation throughout the body are the cause of this syndrome. The syndrome earned its name because one of the common cutaneous signs is a rash that looks like candle wax drips.

Typically, biologic medicines or corticosteroids drugs that inhibit the immune system's

Reactions are used to treat CANDLE syndrome by controlling its symptoms. It's critical that those who have this illness obtain continuing medical attention to monitor and treat them [1].

2. History

In 2010, CANDLE syndrome was identified [1]. They described four children, two of whom were siblings, who were gathered from two facilities in Madrid and Chicago. The children had noticeable skin lesions that, upon histology, exhibited an infiltrate of immature, myeloid, mononuclear cells that resembled leukemia cutis. Because in numerous places of the skin biopsies there was some maturation into polymorphonuclears and karyorrhexis, a sort of yet undescribed “neutrophilic dermatosis” was suspected. Although there was always some degree of skin involvement, the skin lesions had

first developed very early in infancy, in outbreaks that followed frequent triggers (particularly cold and viral infections). Additionally, beginning very early in childhood, the patients experienced frequent fevers or temperature increases below 38.3°C, nearly every day. After more than ten years of follow-up, the majority of patients were emaciated and had a noticeable decrease of body fat, suggesting that the condition caused some overall development delay. An acronym was created to describe the persistent eruption, fevers, lipodystrophy, and cutaneous neutrophilic and

mononuclear immature infiltration. Because they had been the most consistent characteristics, the dermatological aspects were highlighted in this description. However, it was noted that the patients had experienced inexplicable inflammatory attacks in a variety of body organs, including the testes, cartilage, joints, and central nervous system (CNS). An autopsy was not conducted, although one of the patients passed away from a bout of "carditis."

A condition known as JMP (Joint Contractures, Muscle Atrophy, Microcytic Anemia, and Panniculitis-induced Lipodystrophy Syndrome) was identified in three adult patients in 2010. The authors focused on the joint and lipodystrophic characteristics associated with panniculitis, but they made no mention of the disease's cutaneous manifestations. They did, however, expect their patients to experience an innate immune system illness [4].

The Japanese literature had previously documented a similar constellation of indications. As "secondary hypertrophic osteoperiostosis with pernio," a syndrome characterized by nodular erythema, elongated and thickened fingers, and emaciation, and "hereditary lipomuscular atrophy with joint contracture, skin eruptions, and hyper-γ-globulinemia," it was first described by Nakajo in 1939 and Nishimura in 1950 [5].

The Japanese authors suggested "Nakajo–Nishimura syndrome" as an eponym for the syndrome. In general, the patients that were reported began with myositis, nodular erythema-like eruptions, a pernio-like rash, and recurrent high fevers in early infancy. Joint contractures and lipoatrophy developed gradually throughout life, mostly on the upper body, giving the face a distinctive look.

Numerous examples from around the globe were published following the description of CANDLE and JMP, as well as the emergence of fresh cases from Japan. Later, it was revealed that the majority of individuals listed under these headings had homozygous or compound heterozygous mutations in the PSMB8 gene, which codes for the immunoproteasome's β5i subunit [2].

Yet some CANDLE syndrome individuals lacked PSMB8 mutations [2]. Additional genetic research revealed that some individuals have digenic heterozygous mutations in two distinct genes encoding subunits, as well as homozygous and compound heterozygous mutations in other proteasome–immunoproteasome subunits [9]. Lastly, a patient of Lebanese descent who was diagnosed with "unknown autoinflammatory syndrome associated with short stature and dysmorphic features" also showed mutations in the proteasome maturation protein (POMP) gene [10]. The three denominations have been referred to by a number of names, including ALDD (autoinflammation, lipodystrophy, and dermatitis) [12] and PRAAS (proteasome-associated autoinflammatory syndrome) [11].

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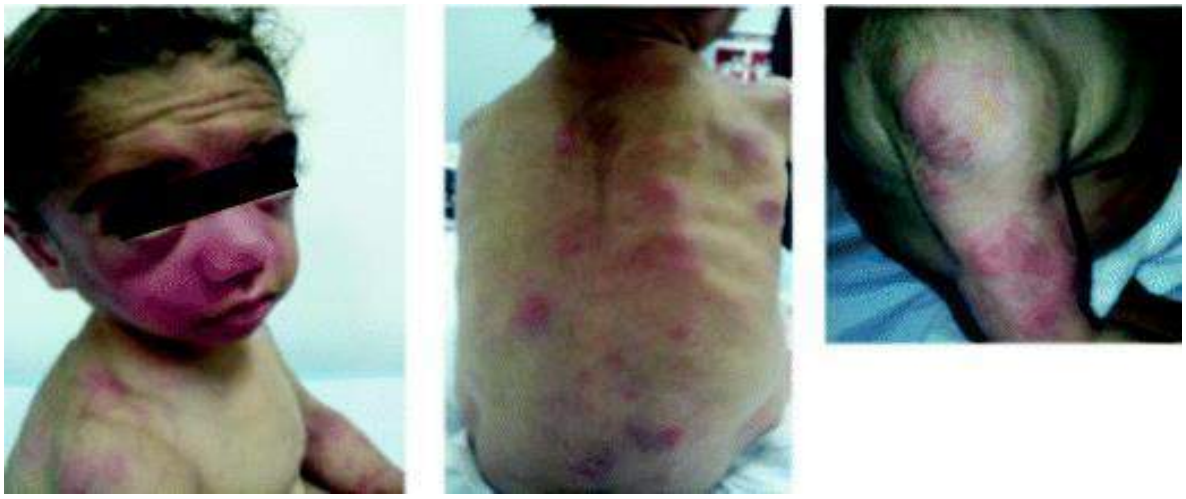
They all refer to the same thing, though, and CANDLE syndrome appears to be the most widely used name. The syndrome's name is emphasized by the patients' overall consumption, which resembles a burnt-out candle.

3. Case Report



A consanguineous couple's straightforward pregnancy ended with the birth of a Eurasian girl at 41 weeks. She had no congenital anomalies and weighed 3015 g at birth. She lost her older brother at the age of ten from purpuric skin nodules, recurring arthritis, and periodic fever. She began to exhibit rashes and a recurring fever at the age of five months. Both bilaterally symmetrical violaceous swollen eyelids and generalized violaceous papules and nodules comprised the skin lesion. Her perioral oedema, hypothyroidism, hepatosplenomegaly, and failure to thrive were initially observed during a 3-year-old hospitalization for pneumonia. She started experiencing active arthritis at the age of four, affecting both large joints (her knees) and minor joints (her hands' PIPs and DIPs). Achilles tendon tension was seen [21].

All therapeutic trials, including CSA, anakinra, etanercept, thalidomide, canakinumab, and taclizumab, were unsuccessful in getting the girl better. Her illness persisted despite her repeated admissions for pulsed methylprednisolone infusion for flare-ups. She was admitted for severe recurring pancreatitis two months after

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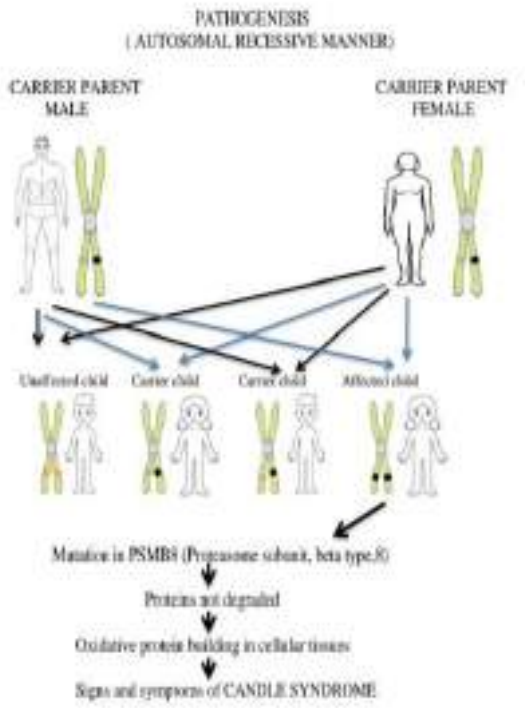
becoming ten years old. The patient passed away in the intensive care unit after developing diabetic ketoacidosis, septic shock, and multiorgan failure. When her homozygosity for the missense mutation c.224C>T in the PSMB8 gene was discovered after her death, a diagnosis of CANDLE syndrome was verified (Goldbach-Mansky R, Translational Autoinflammatory Disease Section, National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, USA) [21].

4. Pathogene



5. Genetic Background

PRAAS are autoinflammatory diseases brought on by aberrant proteasomes. Nakajo-Nishimura syndrome (NNS), panniculitis-associated lipodystrophy (JMP) syndrome, joint contractures, muscle atrophy, microcytic anemia, Japanese autoinflammatory syndrome with lipodystrophy, and the CANDLE syndrome [9,22,23]. PRAAS illnesses are caused by mutations in the PSMB8 gene, which codes for the immunoproteasome's β5i component, as well as other immunoproteasome variants [9,24,25]. Due to gene mutations that cause aberrant proteasome function and disturbance of proteostasis (proteome homeostasis), these disorders have many comparable clinical features [22]. Type 1 interferons (IFN-1) are continuously produced when the immunoproteasome's catalytic activity is compromised, and even minimal stimuli can significantly increase their production [1,21,26]. When a virus infects a cell, the key protein STING (stimulator of interferon genes) is activated due to the presence of viral genetic material in the cytoplasm. IFN-1 genes are transcribed as a result of this activation, and IFN-1s are subsequently released. Many waste proteins are produced when IFN-1s activate the IFN-1 receptor; they must be removed by the proteasome as well as the IFN-1-induced immunoproteasome. Furthermore, the proteasome system must eliminate viral proteins produced by virus-infected cells. Type 1 IFNs may also be released in response to other stimuli that cause cellular stress. Waste proteins build up inside the cell and continue to get ubiquitinated if the proteasome machinery is not

operating correctly. Poly-ubiquitinated protein accumulation intensifies cellular stress and encourages further type 1 IFN synthesis, so sustaining an inflammatory cycle [26]. Cells in CANDLE syndrome are unable to effectively eliminate waste proteins due to malfunctioning of the proteasome system. Even in the absence of outside stressors, this can lead to a mild to severe state of inflammation. However, the need for waste protein elimination during stressful situations—like colds, viral infections, or physical stress—exceeds the compromised proteasome system's capacity [26]. CANDLE syndrome is caused by allelic, monogenic, or digenic double heterozygous mutations in genes producing proteasome or immunoproteasome subunits, with biallelic pathogenic PSMB8 variations being the most common reason. Genes like PSMB8, PSMA3, PSMB4, and PSMB9 are involved in digenic mutations that cause the condition, whereas compound heterozygous mutations may involve PSMB4, PSMB8, and PSMG2. Furthermore, although they are less frequent, autosomal dominant loss-of-function mutations in POMP can also result in CANDLE syndrome [27]. The PSMB8 gene on chromosome 6p21.32 included the first gene mutations discovered in people with CANDLE syndrome. The immunoproteasome's β5i (i=inducible) subunit is encoded by this gene. PSMB8 mutations have been connected to JMP, NNS, and CANDLE syndrome. Later, it was shown that patients with CANDLE syndrome had mutations in other genes, such as those encoding the regulatory protein POMP or distinct proteasome–immunoproteasome subunits. This increased the number of genotypes linked to CANDLE syndrome. All of the discovered mutations were found in vertebrate areas that were highly conserved, indicating that they were harmful.

Patients with CANDLE syndrome have been found to have the following mutations:

1. The production of the β7 subunit within the proteasome is impacted by mutations in the PSMB4 gene, which is located on chromosome 1q21 and codes for the proteasome subunit β type-4. This subunit is necessary for the proteasome complex to properly assemble and maintain its structural integrity, which guarantees that it can break down proteins.
2. PSMA3 mutations: The α7 subunit of the proteasome is produced by changes in the PSMA3 gene (proteasome subunit, α-type, 3), which is located on chromosome 14q23.1. This subunit aids in the breakdown of proteins and is essential to the formation and operation of the proteasome complex. Two mutations affecting the PSMA3 gene have been identified in people with CANDLE syndrome.
3. PSMB8 mutations: Alterations in the PSMB8 gene (proteasome subunit β type-

8), situated on chromosome 6p21.32, control the production of the β5i subunit of the immunoproteasome.

6. Clinical Manifestations

CANDLE syndrome usually starts in the first months of life [1, 28]. Fever or temperature increases below 38.3°C are the most frequent presenting symptoms. These occur every day or nearly every day, yet the overall state is unaffected or even normal. Exposure to cold can occasionally cause skin sores and temperature increase. The earliest clinical manifestation of CANDLE is a skin lesion, which is often present throughout the course of the disease, though it may become less noticeable after puberty. Typically, lipodystrophy begins in early childhood and is well-established before to puberty. Lastly, debilitating joint symptoms typically develop with time. Different acute disease episodes may occur during a patient's lifetime, either on their own or in response to common triggers, and they may impact almost all of the body's organs [25].

The diagnosis of CANDLE syndrome should be made because of the distinctive skin lesions. A quick diagnosis of CANDLE should be possible due to the combination of fever, common skin lesions, and traditional histopathologic findings.

There are three categories of skin lesions in CANDLE syndrome [1,25].

1. Perniotic, acral lesions. These are not frequently observed in childhood or later and typically manifest in neonates and babies. They are characterized by severe, edematous, red or purplish plaques that are primarily found on the nose, ears, fingers, or toes. These lesions may be brought on by cold, although frequently there is no prior history of exposure to cold.

2. Anular plaque: These erythematous or purpuric edematous lesions, which typically have an annular form with elevated borders and a flat, purpuric center, typically begin in infancy or youth. They can develop alone or in crops, and they usually disappear in a few days or weeks, leaving behind a purpuric macule. Over time, remaining purpuric macules coexist with new, active lesions, giving the patients a very recognizable appearance. During youth, these lesions are quite noticeable; however, as people age, they may become less noticeable or even disappear in cases of chronic illness.

3. Periocular and Perioral edema : Infancy or childhood, patients with CANDLE experience a persistent erythematous to violaceous edema that affects the periorbital and, less frequently, the perioral region. In chronic diseases and after puberty, it could be less noticeable.

Early identification of CANDLE may be possible due to the distinctive histological characteristics of the skin lesions [1,25,28]. A variable-intensity perivascular and interstitial infiltration of the papillary and reticular dermis extends to the subcutaneous fat as lobar panniculitis. Since mononuclear cells make up

the majority of the infiltration and many of them have large, irregularly shaped nuclei, the infiltrate's unusual appearance could result in a skin cancer diagnosis. A few mature lymphocytes, few eosinophils, and mature neutrophils are also present in the infiltrate. Leukocytoplasia is frequently observed without vascular fibrinoid necrosis [25, 28]. According to immunohistochemistry, the infiltration is mixed, with a significant number of macrophage cells (positive for CD163 and CD68/PMG1) and myeloid cells (positive for myeloperoxidase). Clusters of CD123-positive plasmacytoid dendritic cells are seen [28].

One of the main signs of CANDLE is fat loss [1,3,29,30]. Although it is gradual and may take several years to fully develop, it is visible in the majority of patients before the age of two. The face is typically where subcutaneous fat loss begins, and it then spreads to the trunk and upper limbs. Usually, the lower limbs are less impacted. Although the exact origin of lipodystrophy is unknown, persistent inflammation of the fatty tissue may be a contributing factor [31, 32]. On the other hand, decreased secretion of adiponectin and leptin and elevated production of proinflammatory cytokines in adipose tissue could be at play [25, 33, 34]. The involvement of IFN in CANDLE disease is further supported by the idea that children with lipoatrophic panniculitis have fat loss linked to a strong type 1 IFN signature. The development of lobar panniculitis with lipophagia and lipoatrophy in patients treated with intramuscular injections of IFN-β suggests that type 1 IFNs may be harmful to adipocytes. [35, 36, 37].

Patients with CANDLE have a distinct phenotype due to lipodystrophy and the usual skin abnormalities. On the face, periorbital and periocular edemas, as well as the loss of cheek fat, are pathognomonic [1]. When combined with significant fat loss, the retracted eyelids and lips in maturity create a fake proptosis and expose the teeth, giving the appearance of being recognizable [4]. Muscle wasting (see later) and gradual fat loss are observed on the limbs. Increased visceral fat, which is still the patient's only source of fat accumulation, may be linked to a protruding abdomen. In CANDLE, a greater separation between nipples is also common [1].

7. Diagnosis

Only a few instances of the typical clinical signs of candle syndrome have been documented in the literature and there are currently no established diagnostic criteria for clinical diagnosis [38,39]. A comprehensive assessment information from physical examinations and further clinical tests are essential to raise suspicions of the illness especially in pediatric patients whose symptoms initially manifest in early childhood the trunk has characteristic annular violaceous plaques. These people

experience fevers of 38.5 C daily or almost daily and they don't respond well to nsaids (non-steroidal anti-inflammatory drugs) during the first few years of life on the basis of such physical examination abnormalities paediatricians or primary care physicians might suspect this syndrome [38, 39]. The majority of patients exhibit violaceous eyelid puffiness, decreased weight and stature, joint pain, elongated clubbed fingers or joint contractures, and progressive lipodystrophy during clinical evaluation and history collection [40, 41].

The primary clinical sign of lipodystrophy is first cutaneous symptoms, and the condition mostly affects the face, cheek, and limb regions. Skin symptoms are among the disease's initial clinical indicators [40]. Annular violaceous plaques, which are frequently brought on by exposure to cold, endure throughout the course of the illness [42]. Characteristics such as perivascular and interstitial infiltrates that extend to the subcutaneous fat as lobar panniculitis, which is mostly made up of mononuclear cells and mature neutrophils, are revealed by biopsy and histological examination of the skin lesions. The characteristic appearance of periocular oedema, common skin lesions, and lipodystrophy is indicative of CANDLE syndrome [40,41].

Common laboratory abnormalities include hyper-c-globulinemia, elevated liver enzymes like alanine aminotransferase and aspartate aminotransferase, elevated acute-phase reactants like C-reactive protein, elevated levels of IFN-1 pathway proteins, and autoimmune hemolytic anemia and pancytopenia. In serological testing, between 40 and 50 percent of patients had positive titers for antinuclear and antiphospholipid antibodies. [43, 44].

8. Treatment

As of yet, there isn't a single, reliable treatment for CANDLE syndrome. Methotrexate and oral corticosteroids may help a little. One may think of methotrexate as the first-line treatment. Fever may be partially controlled with NSAIDs. Colchicine and dapsone have not worked. Intravenous immunoglobulins, azathioprine, or cyclosporine have produced little to no improvement. Etanercept and other anti-TNF medications have not been beneficial and have even exacerbated illnesses [1]. For CANDLE syndrome, a compassionate use therapy strategy has been initiated with baricitinib, a selective JAK1/2 kinase inhibitor. Patients who needed high doses of corticosteroids or who were unable to maintain control were treated with oral baricitinib. Clinical and analytical improvements were observed in eight individuals treated with this medication; however, confirmation of these findings is still pending [45].

9. Conclusion

New insights into the genetics and pathophysiology of CANDLE syndrome have been made possible by the recent identification of the illness and the thorough examination of published cases. However, the genotype-phenotype connections of CANDLE syndrome are yet unclear, and the clinical course and spectrum of organ involvement differ greatly amongst patients. The quality of life and survival of the afflicted patients depend on early diagnosis and treatment, which may be facilitated by identifying the cutaneous abnormalities with distinctive histological results. Along with other focused interventional techniques that might emerge with the goal of assisting clinical management, baricitinib represents a novel and promising treatment.

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