

REVIEW PAPER

CANDLE syndrome – a narrative review

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ABSTRACT

CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a rare autoinflammatory disorder beginning in early childhood. This narrative review provides an extensive overview of CANDLE syndrome, including its epidemiology, aetiology, clinical manifestations, diagnostic challenges, and current treatment options. The syndrome is associated with gene mutations encoding proteasome or immunoproteasome subunits, particularly *PSMB8*, contributing to disrupted proteostasis and aberrant type 1 interferon production. The diagnostic criteria remain undefined, necessitating a multidisciplinary approach for accurate diagnosis and management. Despite therapeutic complexities, recent advancements in genetic testing and targeted therapies, notably Janus kinase inhibitors, offer promising avenues for improved patient outcomes. Further research and clinical trials are imperative to enhance understanding and optimise treatment strategies for this rare and debilitating condition.

KEY WORDS:

fever, dermatosis, lipodystrophy, CANDLE syndrome.

INTRODUCTION

The chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is categorised as a proteasome-associated autoinflammatory syndrome (PRAAS) [1–3]. It is an extremely rare autoinflammatory disorder that typically begins in early childhood [4, 5] and was first described in 1939 by Nakajo, a medical professional at Tohoku University in Japan [1–3]. This syndrome was initially documented in 4 patients exhibiting distinctive clinical, histopathological, and laboratory characteristics in 2010 by Torrelo *et al.* [3, 6, 7]. In the same year, the acronym CANDLE was proposed for the described clinical cases [7, 8]. Patients with CANDLE syndrome are positive for *PSMB8* gene mutation; however, other mutations in other closely related genes are also possible [3, 5, 9–11]. This condition

is characterised by recurrent fevers, skin lesions, lipodystrophy (loss of fatty tissue), and various systemic symptoms [5]. If left untreated, the disease can lead to serious disability and even death. This review provides an extensive overview of CANDLE syndrome, including its epidemiology, aetiology, clinical presentation, diagnostic approach, and current treatment options.

MATERIAL AND METHODS

We conducted a literature search of the MEDLINE database in March 2024, utilising keywords including ‘CANDLE syndrome’, ‘dermatosis’, ‘lipodystrophy’, and ‘fever’ to identify pertinent documents. Initially, 90 records were identified. After title and abstract screening, 41 articles were assessed in full text and ultimately, 40 studies met the inclusion criteria. The inclusion criterion

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was that the article addresses the following issues: a general overview of CANDLE syndrome in the paediatric population, its clinical characteristics, diagnostic pathway, genetic and immune mechanisms leading to CANDLE syndrome, and available treatment methods including the newest targeted therapies. Articles not in English language, without full-text available, and publications not addressing the issues described in the inclusion criteria were excluded from the analysis.

EPIDEMIOLOGY

CANDLE syndrome is an exceedingly rare condition, with fewer than 100 cases reported globally [12]. Clinical manifestations usually begin in the first year of life, especially in the first month [13, 14]. Premature death resulting from sudden occurrences such as infections, cardiomyopathy, and cardiac arrhythmias has been reported [12].

AETIOLOGY

Autoinflammatory disorders caused by abnormal proteasomes are referred to as PRAAS. Examples of PRAAS include Japanese autoinflammatory syndrome with lipodystrophy, Nakajo-Nishimura syndrome (NNS), joint contractures, muscular atrophy, microcytic anaemia, panniculitis-associated lipodystrophy (JMP) syndrome, and CANDLE syndrome [10, 15, 16]. Mutations in the *PSMB8* gene, encoding the $\beta 5i$ subunit of the immunoproteasome, along with other immunoproteasome mutations, cause diseases classified as PRAAS [12, 16, 17]. These conditions share numerous similar clinical characteristics due to mutations that lead to abnormal functioning of the proteasome and disruption of proteostasis (proteome homeostasis) [15]. Malfunctions in the catalytic function of the immunoproteasome result in the continuous generation of type 1 interferons (IFN-1), which can be substantially heightened by even minor stimuli [3, 14, 18].

When a cell is infected by a virus, the presence of viral genetic material in the cytoplasm triggers the activation of the central protein STING (stimulator of interferon genes). This activation leads to the transcription of *IFN-1* genes and the subsequent release of IFN-1s. Activation of the IFN-1 receptor by IFN-1s induces the production of numerous waste proteins, which must be cleared by both the proteasome and the IFN-1-induced immunoproteasome. Additionally, cells infected by viruses produce viral proteins that also need to be removed by the proteasome system. Additional stimuli inducing cellular stress can also result in the release of type 1 IFNs. If the proteasome system is not functioning properly, waste proteins accumulate within the cell and undergo further ubiquitination. The build-up of poly-ubiquitinated proteins exacerbates cellular stress and promotes even more type 1 IFN production, thus perpetuating a cycle of inflammation [18]. In CANDLE syndrome, dysfunction of the proteasome

system prevents cells from efficiently disposing of waste proteins. This can result in a mild to moderate state of inflammation even without external triggers. However, during periods of stress such as colds, viral infections, or physical stress, the demand for waste protein removal exceeds the capacity of the defective proteasome system [18].

Allelic, monogenic, or digenic double heterozygous mutations in genes encoding proteasome or immunoproteasome subunits are responsible for CANDLE syndrome, with biallelic pathogenic *PSMB8* variants being the most frequent cause. Digenic mutations causing the disease involve genes such as *PSMB8*, *PSMA3*, *PSMB4*, and *PSMB9*, while compound heterozygous mutations may include *PSMB4*, *PSMB8*, and *PSMG2*. Additionally, autosomal dominant loss-of-function mutations in *POMP* can also lead to CANDLE syndrome but are less common [19]. To date, only one case of a patient with this mutation has been diagnosed [16].

The initial gene mutations identified in individuals with CANDLE syndrome were found in the *PSMB8* on chromosome 6p21.32. This gene encodes the $\beta 5i$ (i = inducible) subunit of the immunoproteasome. Mutations in *PSMB8* were linked to CANDLE syndrome, as well as *JMP* and *NNS*. Subsequently, mutations in other genes were discovered in CANDLE syndrome patients, including those encoding different proteasome-immunoproteasome subunits or the regulatory protein *POMP*. This expanded the range of genotypes associated with CANDLE syndrome. All identified mutations were located in highly conserved regions across vertebrates, suggesting their pathogenic nature.

The following mutations have been identified in patients with CANDLE syndrome:

- *PSMB4* gene mutations: Alterations in the *PSMB4* gene (proteasome subunit β type-4), found on chromosome 1q21, impact the formation of the $\beta 7$ subunit within the proteasome. This subunit is essential for the proper assembly and structural integrity of the proteasome complex, ensuring its functionality in degrading proteins;
- *PSMA3* mutations: Variations in the *PSMA3* gene (proteasome subunit, α -type, 3), situated on chromosome 14q23.1, govern the production of the $\alpha 7$ subunit of the proteasome. This subunit plays a key role in the structure and function of the proteasome complex, aiding in the breakdown of proteins. Two mutations have been documented in individuals diagnosed with CANDLE syndrome, affecting the *PSMA3* gene;
- *PSMB8* mutations: Alterations in the *PSMB8* gene (proteasome subunit β type-8), situated on chromosome 6p21.32, control the production of the $\beta 5i$ subunit of the immunoproteasome. Mutations in *PSMB8* associated with CANDLE syndrome can disrupt chymotrypsin activity or impede the assembly or maturation of the immunoproteasome;
- *PSMB9* mutations: Changes in the *PSMB9* gene (proteasome subunit β type-3), found on chromosome 6p21.32,

regulate the production of the $\beta 1i$ subunit of the immunoproteasome;

- *POMP* mutations: Alterations in the *POMP* gene, situated on chromosome 13q12.3, govern the production of POMP protein, which plays a critical role in the maturation and assembly of proteasome subunits.

In a solitary case of CANDLE syndrome, a patient was identified without mutations in proteasome subunit genes. Instead, they exhibited a heterozygous, dominant insertion in *POMP*, resulting in a truncated protein likely to be unstable. Insufficient POMP leads to the accumulation of proteasome precursors, diminished formation of mature proteasomes, and overall reduction in proteasome activity [18].

Recently, new mutations in the *PSMB10* and *PSMG2* genes have been discovered to affect either the immunoproteasome directly or general parts of the proteasome subunits or their assembly. These mutations can be a novel cause of CANDLE [9, 20, 21].

SYMPTOMS AND DIAGNOSIS

So far, there have been limited instances documented in the literature showcasing the typical clinical characteristics of CANDLE syndrome, and there are currently no established diagnostic criteria for clinical diagnosis [22, 23]. A comprehensive overview and information from physical examinations and additional clinical tests are essential to raise suspicion of the disease, especially in paediatric patients, where the symptoms are observed in early childhood. These patients present daily or almost daily fevers higher than 38.5°C, with poor response to NSAIDs (non-steroidal anti-inflammatory drugs) in the first few years of life, and characteristic annular violaceous plaques on the trunk are observed. Such abnormalities on physical examination should lead primary care physicians or paediatricians to suspect this syndrome [22, 23].

During clinical assessment and history-taking, most patients present violaceous swelling of eyelids, diminished weight and stature, joint pain, elongated clubbed fingers or joint contractures, and progressive lipodystrophy [4, 5, 7, 8, 12, 24–31]. Notably, lipodystrophy predominantly affects the facial, cheek, and limb regions, with initial cutaneous manifestations being the primary clinical indicator. The first clinical signs to appear in the disease involve skin manifestations [4, 7, 24, 29]. Annular violaceous plaques, often induced by cold exposure, persist throughout the disease trajectory [32]. Biopsy with histopathological scrutiny of the skin lesions reveals characteristic features, including perivascular and interstitial infiltrates extending to the subcutaneous fat as lobar panniculitis, predominantly composed of mononuclear cells and mature neutrophils. The distinctive phenotype of lipodystrophy, typical skin lesions, and periocular oedema is pathognomonic of CANDLE syndrome [4, 5, 7, 14, 23, 32, 33]. Additionally, most patients harbour mutations in

genes that determine the proper functioning of the proteasome, prompting consideration of genetic testing for confirmation [4, 5, 8, 20, 23, 26, 27, 29, 34]. Moreover, testing both parents may be required to confirm digenic inheritance [19]. Laboratory anomalies commonly include autoimmune haemolytic anaemia and/or pancytopenia, elevated liver enzymes such as alanine aminotransferase and aspartate aminotransferase, heightened acute-phase reactants such as C-reactive protein, high levels of proteins of the IFN-1 pathways, and hyper-c-globulinaemia. Approximately 40–50% of patients demonstrated positive titres for antinuclear antibodies and antiphospholipid antibodies in serological tests [4, 5, 8, 24–29, 35, 36]. These findings underscore the diagnostic utility of laboratory investigations [5, 23, 24].

Moreover, with prolonged illness duration and chronic inflammation, internal organ manifestations may emerge. Hepatomegaly of varying degrees is common, as well as hepatic steatosis, which is probably secondary to metabolic disturbances from extensive lipodystrophy, while splenomegaly and generalised lymphadenopathy reflect persistent autoinflammatory activity [8, 24, 25, 27, 29, 32, 35]. During the first decade of life, nearly half of patients develop systemic arterial hypertension [31, 37]. Muscle involvement is also typical, with magnetic resonance imaging often revealing acute inflammatory myositis and disease-related organ involvement [8, 24, 25, 27, 29, 32, 35]. Furthermore, numerous studies underscore the pivotal role of CT (computed tomography) scans in identifying dense bilateral basal ganglia calcifications, further emphasising the necessity of such examinations [4, 24, 27, 29].

The pivotal role of paediatricians and primary care physicians in disease diagnosis cannot be overstated because, based on characteristic symptoms, they can order basic laboratory tests and refer patients to appropriate specialists [12, 35].

TREATMENT

Thus far, no singular treatment has consistently demonstrated efficacy in managing CANDLE syndrome [4, 5, 12, 23, 32, 38]. While oral corticosteroids and methotrexate may offer some relief, responses to steroid-sparing agents have been variable due to the chronic inflammatory nature of the condition, often necessitating high-dose prednisone and organ-specific therapy for most patients [4, 5, 33, 38]. Despite hopes, anti-TNF drugs have proven ineffective, and the Tripathi *et al.* study even showed an exacerbation of the disease [5, 24, 33]. Nevertheless, while disease-modifying anti-rheumatic drugs also failed to reduce corticosteroid dependency, Yamazaki-Nakashimada *et al.* reported improvement in liver function test values and skin lesions after initiating tocilizumab [23, 24, 30, 34]. Whole-genome expression analysis of peripheral blood has pinpointed a highly dysregulated IFN-1 pathway, offering a potential target for

TABLE 1. Overview of genetic, clinical, and therapeutic data for CANDLE syndrome

Category	Details
Genetics	Mutations: CANDLE syndrome is caused by mutations in genes encoding proteasome or immunoproteasome subunits, such as <i>PSMB8</i> , <i>PSMA3</i> , <i>PSMB4</i> , <i>PSMB9</i> , and <i>POMP</i> . New mutations in the <i>PSMB10</i> and <i>PSMG2</i> genes can be a novel cause of CANDLE syndrome Mutation effects: These mutations disrupt the normal function of the proteasome, leading to the accumulation of waste proteins and chronic inflammation
Clinical symptoms	Early onset Fever: Daily or almost daily fevers higher than 38.5°C Skin lesions: Characteristic annular violaceous plaques on the trunk, violaceous swelling of eyelids, and persistent skin manifestations throughout the disease Lipodystrophy: Progressive loss of fatty tissue, especially on the face and limbs Joint issues: Arthralgia and arthritis Systemic symptoms: Diminished weight and stature, hepatosplenomegaly, generalised lymphadenopathy, acute inflammatory myositis Laboratory abnormalities: Autoimmune haemolytic anaemia, elevated liver enzymes, increased ESR and CRP
Available treatments	Corticosteroids: Oral corticosteroids may offer some relief, but high-dose prednisone is often necessary Disease-modifying drugs: Methotrexate and other steroid-sparing agents have variable responses Anti-TNF drugs: Ineffective and may exacerbate the disease JAK inhibitors: Baricitinib, ruxolitinib, tofacitinib, were provided in clinical trials and reported to be highly efficacious, with few side effects Physical therapy: Essential to enhance functionality and prevent joint contractures

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate

novel treatments [12, 20, 26]. In terms of therapeutic efficacy, Janus kinase (JAK), which impedes the transduction of IFN-1-mediated signals on the IFN-1 receptors and of other class I and class II cytokine receptors, has shown promising outcomes [18, 20, 28, 32, 38, 39]. Because the major signalling pathway activated by IFNs is the JAK transducer and activator of the transcription pathway, drugs such as baricitinib, ruxolitinib, and tofacitinib inhibit this pathway and represent a therapeutic opportunity. These inhibitors have demonstrated benefits in alleviating symptoms, reducing IFN-1 scores, and leading to significant improvements, including pain reduction and halting progressive lipoatrophy [18, 20, 32, 38, 39]. The Gómez-Arias study reported that the addition of tofacitinib enabled a reduction in prednisone usage during treatment [29]. Of note is also baricitinib, the effectiveness of which in CANDLE syndrome therapy was found in more than 80% of the patients, with 50% achieving remission despite no corticosteroid treatment [36]. It is essential to incorporate physical therapy in conjunction with oral therapy to enhance everyday functionality and prevent joint contractures [32]. Despite the necessity for confirmation regarding the efficacy of JAK inhibitors, numerous studies have demonstrated promising outcomes in the therapeutic effectiveness of this approach [4, 40]. These findings will be duly considered in the formulation of future standards of paediatric care, underscoring the pivotal role of JAK inhibitors as a promising treatment modality in the foreseeable future [36, 38].

A summary of the aforementioned data concerning genetics, clinical symptoms, and therapeutic approaches, based on original studies, is presented in Table 1 [3, 4, 7, 9, 11, 16, 20, 24].

CONCLUSIONS

CANDLE syndrome is presented as a rare and challenging autoinflammatory disorder [5, 6]. With its recent discovery, understanding its epidemiology, aetiology, clinical manifestations, and treatment options remains limited, but this is crucial for effective management. Despite diagnostic and therapeutic complexities, advancements in genetic testing and emerging targeted therapies, particularly JAK inhibitors, offer hope for improved outcomes [17, 21]. A multidisciplinary approach encompassing comprehensive patient evaluation, genetic testing, and tailored treatment strategies is essential in addressing the complex nature of CANDLE syndrome and enhancing patient quality of life [5]. Further research and clinical trials are needed to advance our understanding and management of this rare condition.

DISCLOSURE

- 1. Institutional review board statement: Not applicable.
- 2. Assistance with the article: None.
- 3. Financial support and sponsorship: None.
- 4. Conflicts of interest: None.

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