MEDDOCS Open Access Publisher

ISSN: 2639-9237

Journal of Case Reports and Medical Images

Open Access | Case Report

Chronic Septic Granulomatosis: About 2 Familial Cases

Rajaa Icharmouhene[1]*; Sara Zizoune[1]; Sanae Azitoune[2]; Chaimae Aoussar[2]; Meryem Zaidouni[2]; Abdelhakim Ourrai[1]; Amal Hassani[1]; Rachid Abilkassem[1]

[1]Department of Pediatrics, Military Hospital Mohamed V of Rabat, Morocco.

[2]Department of Pediatrics, Children's Hospital of Rabat, Morocco.

***Corresponding Author(s): Rajaa Icharmouhene**

Department of Pediatrics, Military Hospital Mohamed V of Rabat, Morocco.

Email: rajaaicharm@gmail.com

Received: Nov 26, 2024

Accepted: Dec 16, 2024

Published Online: Dec 23, 2024

Journal: Journal of Case Reports and Medical Images

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Abstract

Chronic Septic Granulomatosis (CSG) is a primary immunodeficiency caused by mutations in the genes of the NADPH oxidase complex, which is essential for innate immunity. This rare condition is characterized by recurrent bacterial and fungal infections, as well as the formation of granulomas affecting various organs. This article presents two familial cases of CSG, genetically confirmed, treated at the Pediatrics Department of Mohammed V Military Instruction Hospital in Rabat. The first case involves an eight-year-old boy with multiple infections and severe complications, including invasive pulmonary aspergillosis and fistulas. The second case is his 22-year-old sister, diagnosed at the age of ten, who was complicated by resistant granulomatous colitis and pulmonary involvement, requiring allogeneic stem cell transplantation with favorable clinical evolution. Both cases highlight the diagnostic and therapeutic challenges associated with this disease in the context of consanguinity. The study emphasizes the importance of specific diagnostic tests, including the NBT test and genetic analysis, for appropriate management. Treatment includes prophylactic antimicrobials and, in severe cases, stem cell transplantation and immunomodulatory therapies.

Introduction

Chronic Septic Granulomatosis (CSG) is a primary immunodeficiency of innate immunity, caused by mutations in one of the five genes coding for the subunits of the NADPH oxidase complex. This rare genetic condition manifests as recurrent bacterial and fungal infections, along with the formation of granulomas and multi-organ involvement. We report here two familial cases of CSG confirmed by genetic analysis, treated at the Pediatrics Department of Mohammed V Military Instruction Hospital in Rabat. This presentation aims to highlight the therapeutic challenges encountered in optimizing the management of this severe disease in our context.

Observation 1

A male child, 8 years old, with a first-degree consanguinity history. In his family history: recurrent gingivostomatitis in the father, a sister (Observation 2), and a cousin who died in a febrile context that was not documented. In his personal history: recurrent pulmonary and ENT infections, with delayed wound healing of a brow arch injury. He was hospitalized for prolonged fever related to invasive thoraco-pulmonary aspergillosis in a very likely immunodeficient condition. The diagnosis of CSG was confirmed by the Nitroblue Tetrazolium (NBT) test, which showed no oxidative burst in neutrophils (no reduction of NBT), and genetic analysis revealed a homozygous mutation in the

Cite this article: Icharmouhene R, Zizoune S,Azitoune S, Aoussar C, Amal H, et al Chronic Septic Granulomatosis: About 2 Familial Cases. J Case Rep Clin Images. 2024; 7(2) : 1158.

NCF1 gene encoding the p47phox protein. Genetic testing of the parents showed a heterozygous deletion of the GT nucleotide. He was treated with Amphotericin B and Flucytosine for 6 months. Due to the extension of swelling, he was transferred to the pediatric immunology, hematology, and rheumatology unit at Necker Hospital, where he received granulocyte transfusions: 5 times a week for 8 weeks, and 6 months of interferon-gamma therapy, with good clinical and radiological progress. Prophylactic treatment with Itraconazole and trimethoprim + sulfamethoxazole was started. During follow-up, he developed several complications in addition to pulmonary aspergillosis, including pulmonary tuberculosis, influenza A, thoracic shingles, perianal abscess, granulomatous colitis, inflammatory process, pelvic collection with anal fistula, active sub-sphincteric fistula, and Dress syndrome.

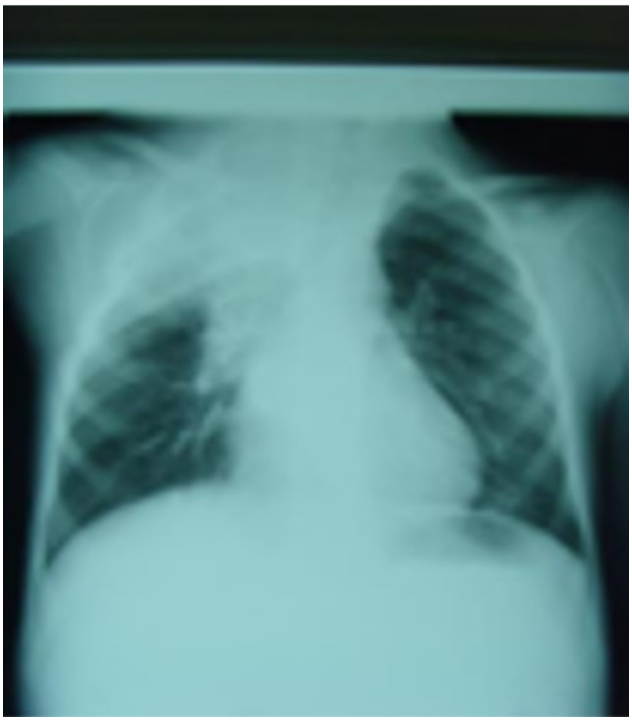

Figure 1: Chest X-ray (frontal view) showing a right upper lobe opacity.

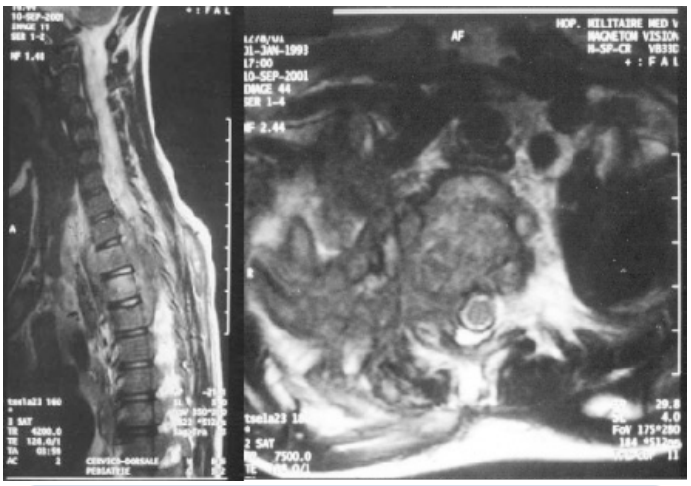

Figure 2: Chest MRI showing the expansive process (transverse and vertical sections).

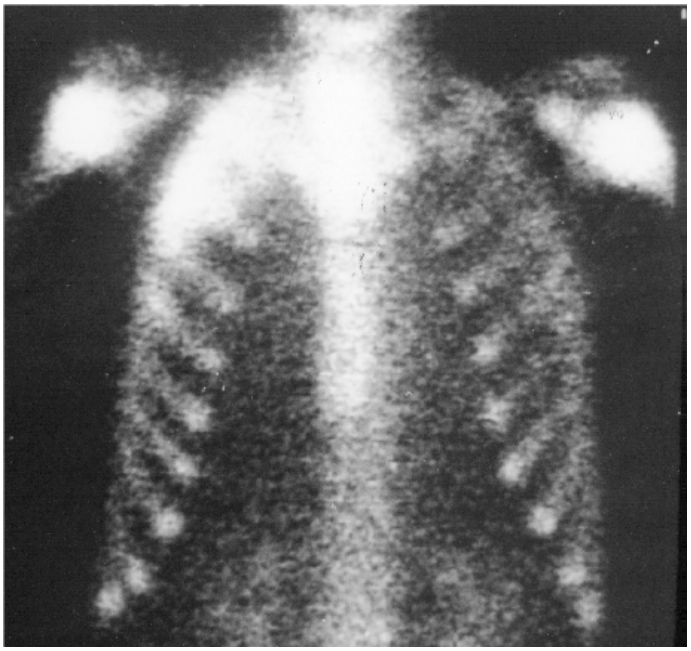

Figure 3: Bone scintigraphy showing intense hyperfixation in the right upper lobe.

Observation 2

K, the sister of M (Observation 1), currently 22 years old, has chronic septic granulomatosis secondary to a homozygous mutation in the NCF1 gene encoding the p47phox protein, diagnosed at the age of 10. She experienced complications, including granulomatous colitis resistant to multiple immunosuppressive treatments, significantly affecting her growth in terms of height and weight, and granulomatous respiratory involvement. She underwent a geno- and pheno-identical allogeneic stem cell transplant at the age of 15 without complications post-transplant. Four years after the transplant, she developed disseminated lupus erythematosus with antiphospholipid syndrome, which had a favorable progression.

Discussion

Chronic Septic Granulomatosis (CSG) was first identified in 1957 by Bridge and colleagues [1] as a fatal disease in children, characterized by recurrent infections, particularly in boys [2]. In 1966, a study showed that neutrophils (PNN) from affected patients had reduced bactericidal activity, which explained the frequency of infections [3]. Starting in 1967, female cases were documented, introducing the concept of mothers as carriers [4].

In 1968 [5], Baehner and Nathan discovered an enzymatic deficiency in the oxidative-reduction system of neutrophils and proposed the Nitroblue Tetrazolium (NBT) reduction test to diagnose the disease. In the same year, an abnormality in the NADPH oxidase enzyme of neutrophils was identified, which explained the dysfunction. In 1969, Douglas and his team observed several types of neutrophil dysfunctions and proposed the first classification of CSG [6].

Chronic septic granulomatosis (CSG) has a global incidence of 1 in 200,000 to 1 in 250,000 live births annually, although this frequency varies depending on consanguinity rates and ethnic specificities of populations [7,8]. X-linked CSG is more common in non-consanguineous populations, while the autosomal recessive form predominates in regions with high consanguinity [9].

The disease primarily affects boys, with a sex ratio of 7 to 1 in favor of males, mainly due to X-linked inheritance [9]. Most cases are diagnosed before the age of five, with an average age of diagnosis ranging from 2.5 to 3 years [10]. Morbidity is marked by severe infections, which are more frequent in patients with the X-linked form, with a mortality rate of 3% per year for this form in specialized centers, compared to 1% for the recessive form [11]. The prevalence of CSG among Primary Immunodeficiencies (PID) varies from 2.7% in Australia to 11.9% in Japan [12].

Chronic Septic Granulomatosis (CSG) is caused by mutations affecting the NADPH oxidase complex, responsible for the antimicrobial defense of neutrophils. This dysfunction leads to impaired microbial destruction, dysregulation of innate immunity receptors, and abnormal formation of NETs (neutrophil extracellular traps), limiting the neutrophils' ability to control infections [13].

Figure 1: Genetic forms of CSG, the involved genes, and their frequencies [14].

Subunit	Genes	Chromosomal Location	Mode of Transmission	Subtype	Designation	Frequency
gp91^phox (Nox2)	**CYBB** Size: 30 kb No. of exons: 13	Xp21.1	X-linked	$X91^{o}$ $X91^{-}$ $X91^{+}$	$CGDX91^{o}$ $CGDX91^{-}$ $CGDX91^{+}$	65%
p22^phox	**CYBA** Size: 8.5 kb No. of exons: 6	16q24	Autosomal recessive	$A22^{o}$ $A22^{+}$	$CGDAR22^{o}$ $CGDAR22^{+}$	< 5%
p47^phox	**NCF1** Size: 15.2 kb No. of exons: 11	7q11.23	Autosomal recessive	$A47^{o}$	$CGDAR47^{o}$	25%
p67^phox	**NCF2** Size: 37 kb No. of exons: 16	1q25	Autosomal recessive	$A67^{o}$ $A67^{-}$	$CGDAR67^{o}$ CGDAR67	< 5%
p40^phox	**NCF4** Size: 18 kb No. of exons: 10	22q13	Autosomal recessive	$A40^{o}$	$CGDAR40^{o}$	1 case

Patients with CSG develop excessive inflammation due to altered production of Reactive Oxygen Species (ROS), which promotes elevated expression of inflammatory mediators. This defect also leads to increased activation of the inflammasome and insufficient efferocytosis, contributing to prolonged inflammation and granuloma formation [14].

Patients with CSG present a heterogeneous clinical picture dominated by recurrent or severe bacterial infections (Staphylococcus aureus, Pseudomonas, Serratia, Nocardia) and fungal infections (Aspergillus, Candida) at preferential sites such as the lungs, skin, lymph nodes, liver, and bones [15]. Inflammatory and granulomatous manifestations are also common, including wound healing abnormalities, hepatosplenomegaly, hepatic granulomas, lymphadenopathy, and gastrointestinal involvement such as granulomatous colitis, strictures, fistulas, as well as cutaneous and mucosal lesions. Early signs include growth delay, delayed cord separation, and delayed umbilical stump fall [16]. It may be associated with autoimmune diseases, such as lupus erythematosus, juvenile idiopathic arthritis, or in the case of McLeod syndrome, which is associated with certain X-linked forms of CSG [16].

The paraclinical diagnosis of Chronic Septic Granulomatosis (CSG) is based on:

Non-specific tests:

✓ **Complete blood count:** May reveal anemia related to chronic disease or vitamin B12 deficiency.

✓ **Protein electrophoresis:** Often shows hypergammaglobulinemia and hypoalbuminemia in some patients.

✓ **Lymphocyte subtyping:** Reduced memory B lymphocytes and CD4 T lymphocytes, without increased risk of infection.

✓ **ESR and CRP:** Usually elevated in cases of inflammation.

Specific tests: A history of severe or recurrent infections leads to the performance of a neutrophil function test. If this test is positive, confirmation is carried out through genotyping, sometimes using immunoblotting to detect the p47phox mutation.

➢ **Functional Diagnosis:**

- **Neutrophil tests:** The dihydrorhodamine 123 (DHR) test, known for its high sensitivity, is commonly used, followed by the Nitroblue Tetrazolium (NBT) test. Other methods such as spectrophotometry, chemiluminescence, and oxygraphy are also available [17].

➢ **Biochemical and Genetic Diagnosis**:

- CSG is confirmed by immunodetection of the mutated protein. Genetic sequencing helps identify mutations, particularly nonsense mutations, which are associated with more severe forms of the disease [18].
- For autosomal recessive forms, family genetic testing and prenatal diagnosis may be considered [19].

In the case of two patients, an NBT test and genetic analysis revealed a homozygous mutation in the NCF1 gene, confirming an autosomal recessive form of CSG, commonly observed in mutations of the p47phox protein.

The treatment of CSG focuses on the prevention and control of infections, as well as supporting the immune system.

➢ **prophylactic Anti-Infective Treatment**:

- **Antibiotics:** Prophylactic antibiotic treatment with sulfamethoxazole-trimethoprim is frequently prescribed to prevent common bacterial infections.
- **Antifungals:** Itraconazole is recommended to prevent fungal infections.

➢ **Immunomodulatory Therapies:**

- **Gamma interferon [13]:** It can be administered to enhance neutrophil function and reduce the frequency of infections. This treatment is particularly useful in some patients to stimulate the immune system.
- **Hematopoietic Stem Cell Transplantation [19]:** This therapeutic option may offer potential cure by replacing deficient cells with healthy ones. It is considered for severe cases and young patients.
- **Gene Therapy [20,14]:** Currently under development to directly correct the genetic mutation responsible for the disease, gene therapy is being considered as an option for patients who do not respond to conventional treatments.

Regular medical follow-up is essential to monitor infections and treat complications promptly.

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