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IMMUNOLOGICAL INVOLVEMENT IN

Congenital Disorders of Glycosylation (CDG)

2018

A community-friendly document

PORTUGUESE ASSOCIATION | CDG

Immunological Involvement in Congenital Disorders of Glycosylation (CDG)

Immunological involvement in **CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)**

A project created and led by the Portuguese Association for CDG (www.apcdg.com) in collaboration with: Working Group (WG) CDG & Glycoimmunology, integrated in CDG & Allies - Professionals and Patient Associations International Network (CDG & Allies- PPAIN, www.researchcdg.com), Faculdade de Ciências e Tecnologias (FCT) from NOVA University of Lisbon (www.fct.unl.pt), and UZ Leuven (www.uzleuven.be).

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CDG Resources
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The Portuguese Association for CDG (APCDG-DMR, www.apcdg.com) seeks to improve the quality of life of patients and family members through awareness, community--building, research, resources, education, empowerment and advocacy.

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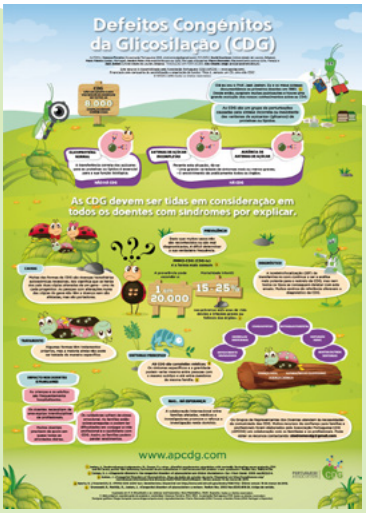
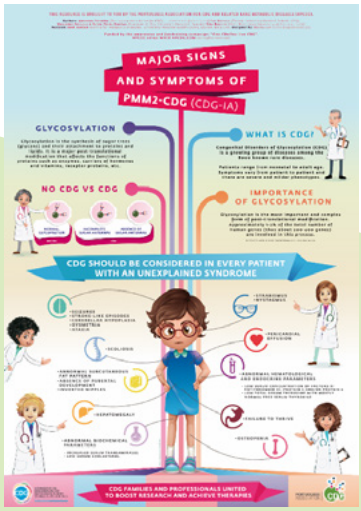
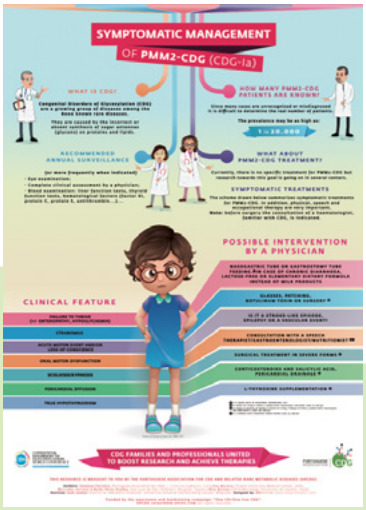






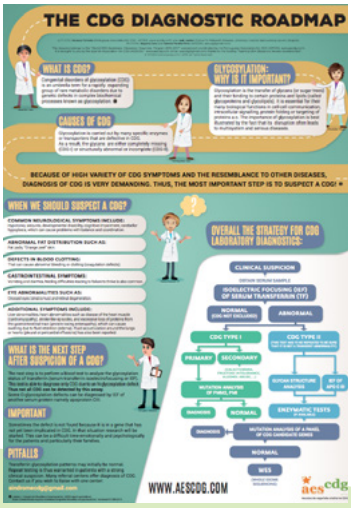
CDG Resources

CDG & ALLIES – PROFESSIONALS AND PATIENT ASSOCIATIONS INTERNATIONAL NETWORK (CDG & ALLIES-PPAIN)

CDG & Allies -PPAIN is a patient-centered, international research network. All research projects are based on the needs and ideas of CDG patients and families. This research network counts with over 45 KOLs, from clinicians, to basic and clinical researchers, other healthcare professionals and families from 8 different countries around the globe.

All the resources, including published scientific papers and posters at:
http://www.researchcdg.com/resources.html

www.researchcdg.com



We know how important patient-friendly documents are for families and professionals.
TOGETHER, WE CAN MAKE IT HAPPEN!

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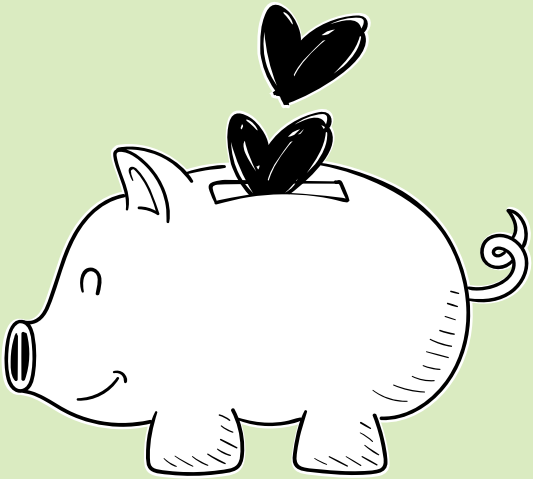

APCDG-DMR is led by affected family members that volunteer in an altruistic manner. We do not receive government funding. We rely solely on donations, in order to continue our projects. Thus, we know how to do a lot with very modest budgets.

We still need your contribution to help us do our work.
If you wish further information, please write us at: sindromecdg@gmail.com

WWW.APCDG.COM

YOUR GENEROSITY HELPS US

Fostering breakthrough research that makes a difference in the lives of CDG patients and their family members (more info and details at www.researchcdg.com). Our actions are performed at the national and international levels.

Exceptional individuals are doing tremendous contributions as volunteers to move APCDG mission forward.

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This community-friendly document was created and led by the Portuguese Association for CDG (www.apcdg.com) in collaboration with Working Group (WG) CDG & Glycoimmunology integrated in CDG & Allies-PPAIN (www.researchcdg.com), Faculdade de Ciências e Tecnologias (FCT) from NOVA University of Lisbon (www.fct.unl.pt), and UZ Leuven (www.uzleuven.be). It summarizes the results from a project entitled ***"Immunological aspects of congenital disorders of glycosylation (CDG): a review."***

Working Group (WG) CDG & Glycoimmunology

The Working Group Leader (WGL) is **Prof Paula Videira** (Associate Professor at Faculdade de Ciências e Tecnologias (FCT) of Lisbon NOVA University and Director of CDG & Allies-PPAIN). The main authors of this patient-friendly document are **Rita Francisco** and **Carlota Pascoal**, in collaboration with **Dr Dorinda da Silva**, **Prof Paula Videira**, **Dr Vanessa Ferreira**, **Prof Fernando Pimentel**, **Prof David Cassiman**, **Prof Jaak Jaeken** and **Prof Eva Morava.**

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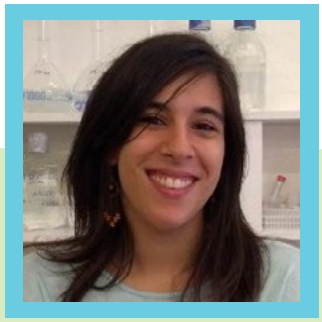

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The International CDG parent advisory committee actively participated in improving the understanding of this document. We are grateful to:

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Meral Omurtag

Merell Liddle

Rana Atwi

Tatiana Rijoff

Immunologists are one of the **MEDICAL SPECIALISTS WHO FOLLOW CDG PATIENTS**

Hi! I am an immunologist. There is still very limited knowledge on how CDG affects the immune system. My colleagues and I, we are still unsure about the causes and clinical signs of immune alterations in CDG patients. This document will raise awareness and education by providing patient-friendly information to the families and specialized information to physicians and other professionals.

WHEN SHOULD I THINK "IT COULD BE CDG"?

1- Any unexplained neurological syndrome, particularly when associated with other organ disease and/or recurrent and severe infections;

2- Any immunological syndrome without a diagnosis;
AND even in:

3- Any unexplained syndrome without neurological involvement.

Table of **CONTENTS**

DISCLAIMER

The information and advice published or made available in this booklet is not intended to replace the services of a physician, nor does it constitute a physician-patient relationship. This advice should be taken in combination with medical advice from your physician, whom you should consult in all matters relating to your health, in particular with respect to symptoms that may require diagnosis or medical attention. Any action on your part in response to the information provided in this booklet is at your own discretion.

01.
WHAT IS THE IMMUNE SYSTEM?

The **immune system** consists of a **network of cells, tissues,** and **organs** that work **together to protect the body** (see Figure 1).

It is responsible for defending our body against microorganisms and unhealthy cells and distinguishes our cells (self) from foreign cells (non-self). Usually, it does a great job at keeping people healthy and preventing infections, but sometimes problems with the immune system can lead to illness and infection.

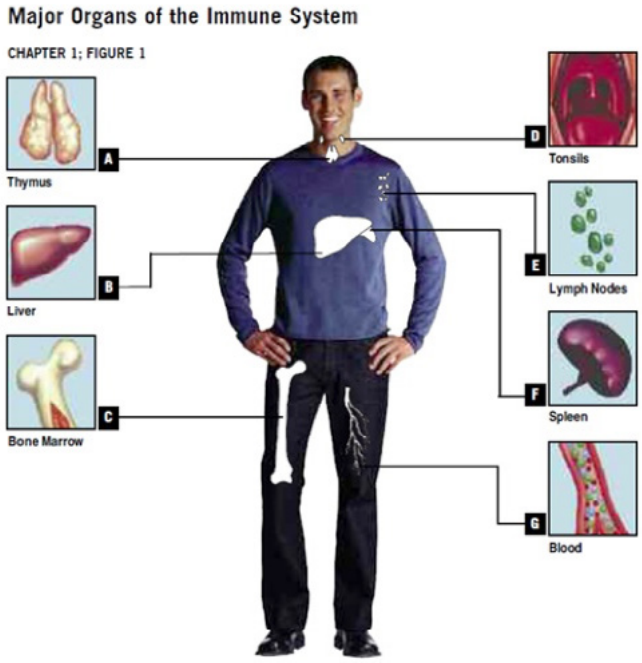


Figure 1 – Major organs of the immune system: Blood, bone marrow, spleen, lymph nodes, liver and thymus. Source https://primaryimmune.org/about-primary-immunodeficiencies/relevant-info/the-immune-system

There are 2 types of immune responses:

Innate immune response

√ Non-specific, first defense immune mechanisms with which we are born;

√ Involves physiological barriers (skin, saliva, gastric acid…) that keep harmful substances from entering the body;

√ Wide and diverse number of cells ready to attack invaders (microorganisms).

Adaptive immune response

√ Delayed response;

√ Mediated by specialized immune cells (B and T cells);

√ Critical to create immunological memory, which is a feature that makes an individual protected against future infections by the same invader (microorganism).

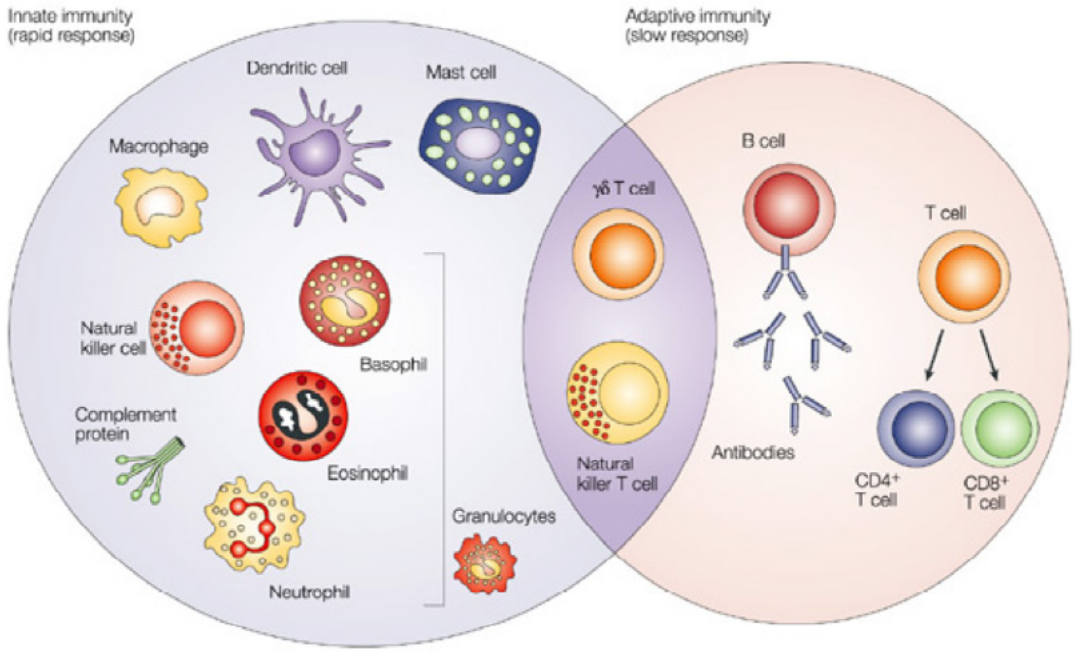


Figure 2 – Cells of the innate and adaptive immune responses. Reference: *Nature Reviews Cancer* 4, 11-22.

02.
HOW DOES THE IMMUNE SYSTEM WORK?

When a microorganism manages to get through our physiological barriers and is detected, innate immune cells (Figure 2- blue circle) **will immediately start working together to recognize it and to respond accordingly, neutralizing or destroying the threat. Innate immune cells will then trigger specialized immune cells (cells from the adaptive response,** (Figure 2 – orange circle)**, namely:**

-B cells (Figure 2- orange circle) to produce antibodies (or immunoglobulins – Ig), which are specialized proteins that bind specifically to a microorganism. There are different types of antibodies (IgG, IgM, IgA, IgE and IgD) with several immune functions.

Figure 3 shows how antibodies fight microorganisms. Importantly, after eliminating an infection, antibodies remain in the organism, and become ready to fight future infections by the same pathogen in a process called immunological memory.

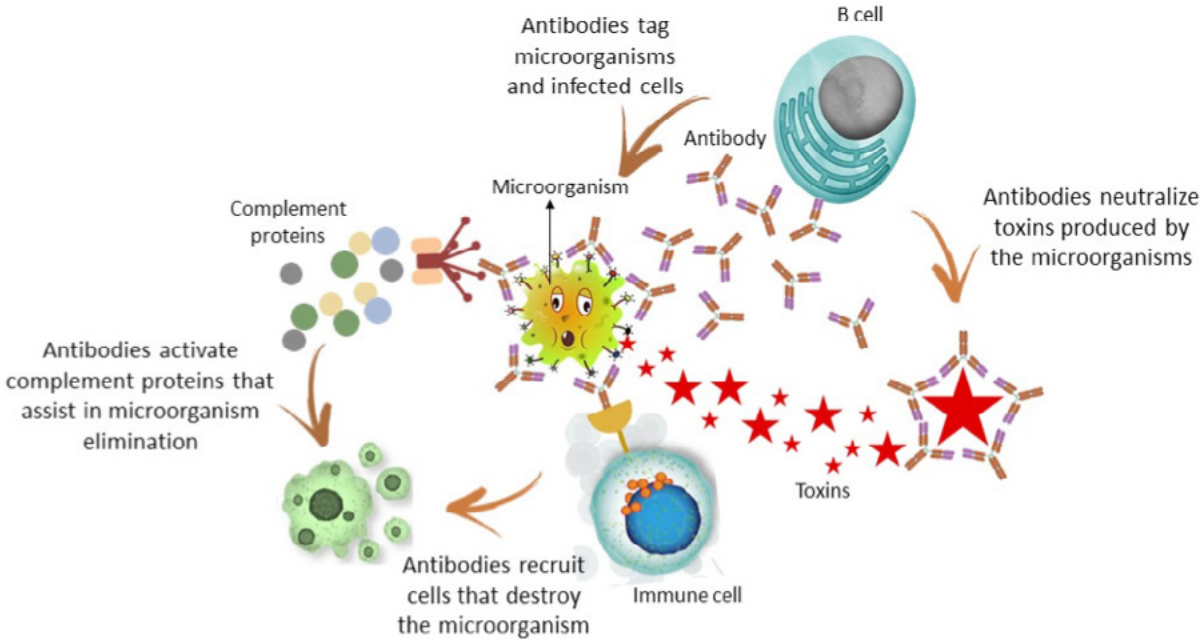


Figure 3 – Antibodies' main functions.

- T cells (Figure 2 – orange circle) **that destroy our cells that have been infected or somehow changed by the microorganisms invading and attacking our body. T cells do this by releasing specific substances and by recruiting other immune cells, like B cells, to act.**

These specialized cells and parts of the immune system offer the body protection against disease, by coordinating their actions and communicating with each other, thus conferring immunity to our bodies.

Figure 4 gives an overview of the immune system's features in a simplified manner.

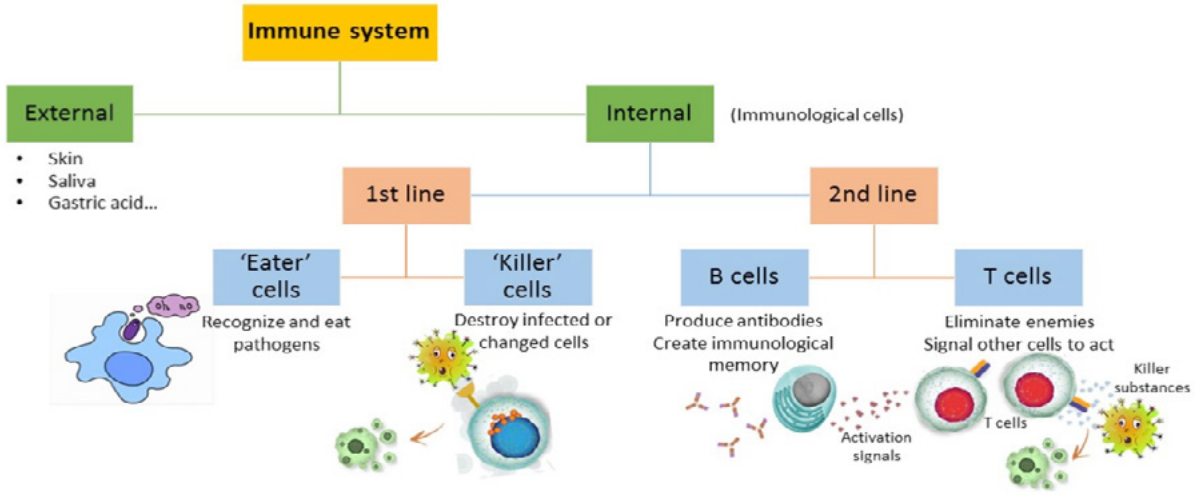
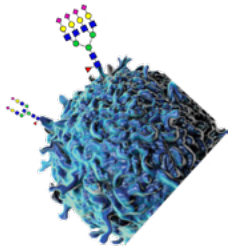


Figure 4 – Overview of the immune system.

03.
WHAT IS GLYCOSYLATION?

Glycosylation is the process through which **“sugar trees”** (or glycans) are assembled and attached to proteins and lipids (fats). Around 50% of all our bodies proteins, present in our cells and organs, are modified with **“sugar trees”**. This modification allows proteins and lipids to acquire their proper function and perform a differentiated role in the cells/organs.



03.1.
HOW DOES IT IMPACT THE IMMUNE SYSTEM?

Glycans play various roles in the **immune system**. Many of the proteins that are part of the immune system are modified with **sugars**, so sugars are important in the recognition of threats as well as in the definition of the intensity and duration of the immune response/reaction. Basically, **protein-attached sugars control when, how** and **for how long the immune system should fight a specific threat.**

Glycan recognition is important in events, such as:

The diversity of glycans that decorate each protein/cell of the immune cells is determinative for several immune processes (see example - Figure 5).

Responsible for pathogen elimination.

Glycan Recognition

Affects the immune cells' migration from blood to tissues (essential to fight infection).

Sialic acid (a type of sugar) helps our cells 'hide' from pathogens and the immune system distinguish between ‘good’ and ‘bad’ cells, and attack only the former.

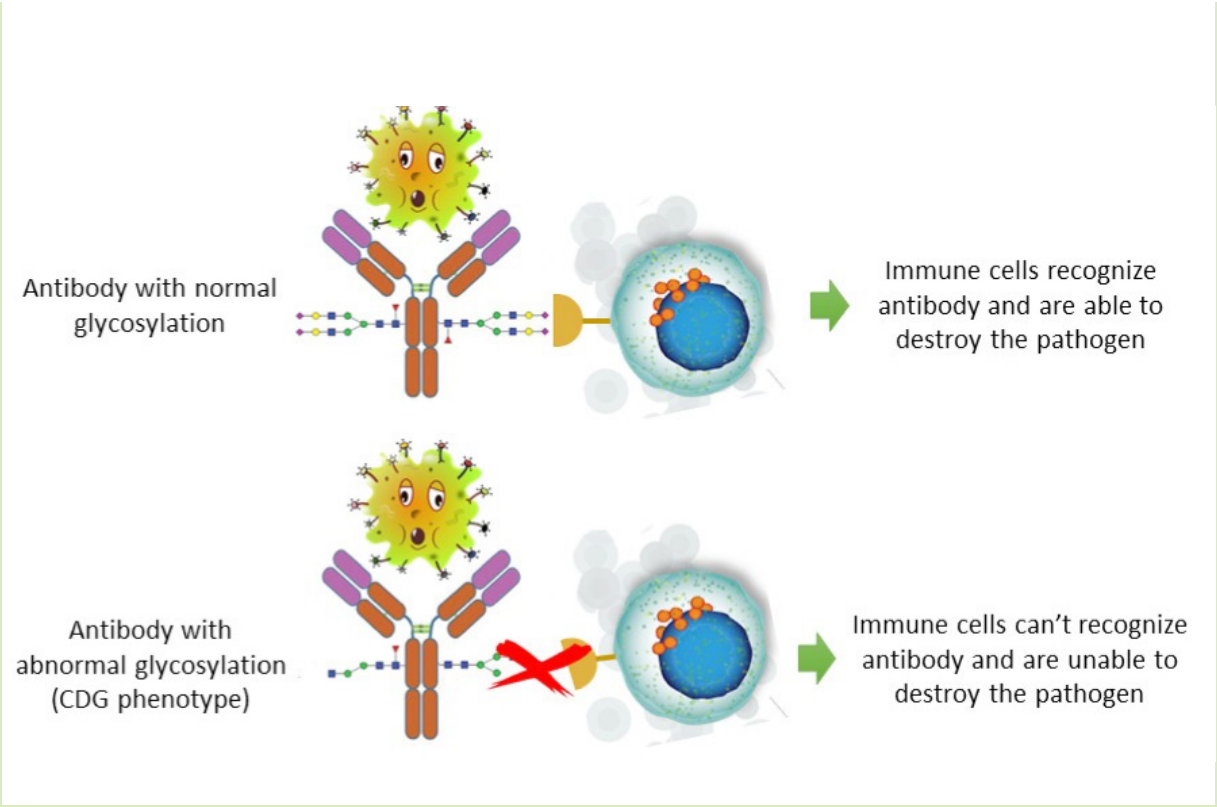


Figure 5 – Glycan recognition. Immune cells bind to antibodies with normal sugars, but fail to recognize abnormal sugars, thus affecting pathogen elimination.

In CDG patients, the mechanisms that attach sugars to proteins and fats are defective, therefore, immune responses may be inefficient and/or altered.

04.
DEFECTIVE GLYCOSYLATION MAY CAUSE THE IMMUNE SYSTEM TO FAIL OR MALFUNCTION: WHAT CAN HAPPEN?

EXAMPLES OF DYSREGULATIONS OF THE IMMUNE SYSTEM, INCLUDE:

√ **Infections –** Infections happen when a microorganism attacks and successfully invades our body. Infections may be:

- √ **Recurrent**, they happen repeatedly and are associated with acute symptoms and clinical manifestations;
- √ **Chronic**, infections that are prolonged or persistent in time and are usually related to less intense immune responses;
- √ **Organ specific**, infections are restricted to a single organ, e.g ear infections, pneumonia, urinary infections;
- √ **Generalized**, infection is present in several organs at the same time, e.g sepsis.

√ **Autoimmune diseases –** When the immune system starts recognizing our own cells as foreign/threats and attacks them, thus harming/destroying them. It's like a self-destruction mechanism.

√ **Allergies –** When the immune system recognizes something that is harmless to most people as a threat (e.g food allergy). Symptoms/signs of allergies include, rashes, trouble breathing, itch or cough, among others.

√ **Altered response to vaccination –** Vaccination may either be ineffective (either protective antibodies do not develop or are rapidly lost) or may trigger (severe) side effects/adverse reactions (e.g infections or allergies).

05.
WHAT IMMUNOLOGICAL ALTERATIONS DO CDG PATIENTS HAVE?

Some Facts

A thorough analysis of the literature allowed us to identify:

√ 13 CDG types, whose patients present with immunological affectations;

√ Among those 13 CDG types, some present immunological problems of major importance (they are the predominant or the most severe clinical feature), while in other types of CDG immunological problems are of minor importance (which means they are usually mild or infrequent);

Table 1 – CDG with major and minor immunological problems.

CDG WITH MAJOR IMMUNOLOGICAL PROBLEMS	CDG WITH MINOR IMMUNOLOGICAL PROBLEMS
ALG12-CDG, MAGT1-CDG, MOGS-CDG, SLC35C1-CDG, PGM3-CDG	PMM2-CDG, MAN1B1-CDG, COG6-CDG, ALG1-CDG, MGAT2-CDG, DOLK-CDG, PIGY-CDG, GALNT3-CDG

CDG with major immunological problems

√ **ALG12-CDG:** High frequency of common infections, pneumonia, and lethal sepsis (a generalized and severe infection that is not adequately controlled by the immune system, thus damaging one's own organs).

√ **MAGT1-CDG:** Impaired capacity for fighting and clearing Epstein-Barr virus (EBV) infections, e.g infectious mononucleosis.

- Treatment: it appears that supplementation with magnesium ions regulates magnesium levels in immune cells and decreases EBV infections. Clinical trials based on these observations are underway.

√ **MOGS-CDG:** Increased resistance to infections with by enveloped viruses (viruses that are covered in a layer made of proteins and sugar) that are dependent on sugars to enter cells, like HIV.

√ **SLC35C1-CDG:** Recurrent infections, inability to produce pus, with an unusually high count and impaired function of specific immune cells.

- Treatment: intake of oral fucose (a sugar) that improves the immune cells count and decreases recurrent infections.

√ **PGM3-CDG:** Recurrent infections (bacterial, viral and fungal), allergy and atopy (this is a predisposition toward developing certain allergic hypersensitivity reactions).

CDG with minor immunological affectations

√ **PMM2-CDG:** Some infants suffer from recurrent and severe infections (sometimes fatal).

- When vaccinated, some patients failed to respond to some of the vaccines and lost the protection conferred by vaccination very soon after inoculation.

- It has been suggested that stroke-like episodes are frequently associated with infections in PMM2-CDG patients.

- Treatment: patients received frequent administration of antibiotics (medicines that fight infections) and antibodies (specific proteins that fight infections) through the vein with some preventive effect.

√ **MAN1B1-CDG:** The antibodies (specific immune proteins that fight infection) of these patients were found to be altered. It is still necessary to find out exactly how these alterations affect the action of the antibodies.

√ **COG6-CDG**: Recurrent infections. An alteration in various immune cell types has been also observed (little or no immune response).

√ **ALG1-CDG:** Patients can suffer from severe infection or unexplained fever.

√ **MGAT2-CDG:** Recurrent infections.

√ **DOLK-CDG:** Recurrent and severe infections and low levels of immune cells.

√ **PIGY-CDG:** Reported patients had enterocolitis (inflammation of the digestive tract), and chronic lung disease.

√ **GALNT3-CDG:** Association with some auto-immune and auto-inflammatory diseases, as vasculitis (destruction of blood vessels), arthritis (joint inflammation) and osteomyelitis (bone inflammation).

06.
WHICH IMMUNOLOGICAL TESTS SHOULD THE CDG PATIENT HAVE?

If the CDG patient suffers from recurrent infections, immunological investigations should be done to understand what is causing that susceptibility/tendency, namely:

Adhesion molecules (e.g. CD11b, CD15, CD18) tests – These tests allow us to determine the levels of each type of immune cell. In this way, it can be established if the cell levels are increased or decreased (compared to reference values), and this can tell us if there is any underlying immunological problem.

C-reactive protein (CRP) – It is a substance produced by the liver in response to inflammation. When the patient has a high CRP count it can indicate infection or autoimmune disease presence.

Challenges with T-dependent antigens and challenges with T-independent antigen – These tests allow to determine if B cells and T cells (see the definition in Chapter 1: "What is the Immune system?" and Chapter 2 "How does the immune system work?") are working properly and communicating well with each other.

Complement factors (CH50, complement fixation assay) test – These assays measure the activity of the complement system. Each component of this system may be analysed, to determine if any is lacking or deficient.

Immunoglobulin (Ig) analysis (e.g. IgG, IgM, IgA, IgE) – Count of Ig (see the definition in the Chapter 2 "How does the immune system work?") levels present in blood. Higher or lower than reference values can be signs of infection and immune deficiency, respectively.

Lymphocyte proliferation assay – This assay measures the capability of lymphocytes (B and T cells) to divide and multiply upon exposure to substances that stimulate division. If the lymphocytes are normal they will divide as expected, in certain immune diseases lymphocytes ability to divide is impaired, thus leading to infections.

Oxidative burst test – The oxidative burst is a crucial chemical reaction that occurs in some immune cells. The release of these chemicals happens when specific immune cells are infected by bacteria or fungi. Therefore, this diagnostic test helps establish if the patient is suffering from an infection.

Phagocytosis test – Some immune cells eliminate invaders (microorganisms) by "eating them", as they engulf and digest the microorganisms. This process is called phagocytosis and it's one of the main innate immune responses. This test determines if this response is occurring, and the cells carrying it out are not impaired.

Leukogram or leukon – It is the count of white blood cells present in blood. Counts that are higher or lower than reference values are indicative of infection and immune deficiency, respectively.

If the CDG patient is suspected to suffer from an autoimmune disease:

Autoantibody tests – Autoantibodies are antibodies that attack one's own body. There are several tests that identify such antibodies, namely **Antineutrophil Cytoplasmic Antibodies (ANCA), Anti-Double Stranded DNA (anti-dsDNA), Anticentromere Antibodies (ACA), Antihistone Antibodies, Cyclic Citrullinated Peptide Antibodies (CCP), Extractable Nuclear Antigen Antibodies (e.g., anti-SS-A (Ro) and anti-SS-B (La), anti-RNP, anti-Jo-1, anti-Sm, Scl-70), Rheumatoid Factor (RF).** There are also autoantibody tests specific for one organ.

Erythrocyte sedimentation rate – This is a simple, non-specific and inexpensive test that detects inflammation associated with infection and/or autoimmune diseases. This assays only measures the rate at which red blood cells sediment (deposit) in a period of one hour.

If the CDG patient is suspected to suffer from allergies:

Skin prick test – This checks for immediate allergic reactions to different substances (e.g pollen, mold, pet fur, dust mites or foods).

To determine the efficacy of vaccination in the CDG Patient:

Antibody titers – This is a test that detects and measures the production of antibodies in the blood.

07.
WHAT THERAPEUTIC STRATEGIES CAN THE CDG PATIENT FOLLOW?

Therapeutic strategies need to be defined and discussed with the attending or specialist physician, and only adopted following confirmed medical diagnosis and recommendation.

If the CDG patient suffers from recurrent infections, some treatment approaches may include:

Antibiotics – A class of medications that treats bacterial infections.

Immune modulators – This is a class of medicines that controls (or modulates) the immune response. They can stimulate/repress the immune response or induce immune tolerance.

Immunoglobulin infusions – Intravenous administration of Ig (also called antibodies). This therapeutic approach helps fight and prevent infection as well as normalize the Ig levels.

If the CDG patient has the confirmed diagnosis of an autoimmune disease, therapies may include:

Anti-inflammatories – A class of medicines that reduces inflammation and swelling.

Immunosuppressive medication – A class of medications that suppresses, reduces or stop the immune response. They are used following transplants, and to treat autoimmune diseases.

If the CDG patient has the confirmed diagnosis of allergies, therapeutic approaches may include:

Anti-histaminics – A class of medicines that treats allergies.

Anti-inflammatories – A class of medicines that reduces inflammation and swelling.

Anti-leukotrienes – A sub-class of anti-inflammatory medicines, which are used to treat diseases related to inflammation of the lungs, such as asthma as well as allergic rhinitis.

Bronchodilators – Medicines that open the airways of the lungs, and are used to treat asthma, allergies or other breathing problems.

Corticosteroids – A class of medicines used to control inflammation or to regulate salt in the body (depending on type of corticosteroid).

08.
CONCLUSIONS OF OUR LITERATURE REVISION

√ At least 10% of all CDG types have immune-related problems;

√ Immunological problems include frequent infections, allergies, autoimmune diseases;

√ CDG patients may show altered response to vaccination;

√ Infections in CDG patients are a significant cause of death, particularly during childhood;

√ In some patients, specific immune cells and proteins are found to be impaired, and/or decreased, which in some cases could explain the immunological signs/symptoms;

√ For the wide majority of CDG there are no targeted treatments for immunological problems;

√ Healthcare professionals are still largely unaware of CDG and of the underlying immunological problems found in these patients;

√ Immunological reports of CDG patients are scarce and not very detailed, which led us to conclude that immunological issues are probably overlooked and in need of better clarification. We hypothesize that more CDG forms and patients have immunological alterations.

√ **However, if sugars are so important for the correct functioning of the immune system, why don't all CDG patients and forms have immunological problems?** *We cannot answer that for sure, but we predict that some patients may develop compensatory defense mechanisms.*

√ CDG should be tested in undiagnosed patients, who present with immunological syndromes and/or recurrent infections associated with altered immune parameters.

Taking into account our findings, we recommend that an immunological check-up should be performed in all CDG patients with and without known immunological problems, so that a greater understanding of the extent and severity of immune alterations in CDG can be achieved.

09.

HOW DID WE COLLECT THE DATA ON IMMUNOLOGICAL INVOLVEMENT IN CDG?

First search

ON PUBMED DATABASE USING:

Keywords related to immunological involvement combined with;

CDG terms.

WWW.NCBI.NLM.NIH.GOV

Second search

ON OMIM WEBSITE WE LOOKED FOR IMMUNE SYSTEM'S DYSFUNCTIONS DESCRIBED FOR EACH CDG TYPE.

WWW.OMIM.ORG

SOME OF THE SELECTION CRITERIA USED TO EXCLUDE THE ARTICLES THAT HAD NO RELEVANCE FOR OUR STUDY.

- No mention of immune disease/parameters;
- No clinical description;
- Unknown CDG type.

Total number of scientific articles used in our revision of literature and that inspired this document = 123

10.

CDG CAN PRESENT AS AN IMMUNOLOGICAL SYNDROME.

The immune problems more commonly and repeatedly reported across CDG types were recurrent infections.

Infections have been reported to be associated with or trigger around 50% of all stroke-like episodes in PMM2-CDG patients.

Infections have been reported as the cause of death in around 20& of PMM2-CDG patients.

However, there are some CDG types that manifest, sometimes exclusively, as an immunological syndrome.

One example is PGM3-CDG, for which bone marrow transplantation is already an approved therapy in the US.

In spite of this,

The underlying cause of most of the CDG types currently known, very often cannot be treated (yet). Immune-related problems can often be treated or prevented with the help of experienced immunologists.

11.

WHAT'S NEXT?

IMMUNOLOGY CDG QUESTIONNAIRE (IMMUNOCDGQ)

Will you be our research partner?

An online survey has been approved by an ethics committee. It aims to better understand immunological involvement in CDG patients and its impact on the patients' well-being. We will gather knowledge in an anonymous and collective manner, directly from the patients and family members. This approach overcomes major obstacles related to research on rare diseases, such as:

- √ Poor understanding of the disease;
- √ Heterogeneous patient populations with variable disease presentation and clinical courses;
- √ Geographic dispersion of patients and researchers;
- √ Difficulty in accessing sufficient and reliable data to draw significant conclusions.

The Immunology CDG Questionnaire (ImmunoCDGQ): A patient-centered approach to better understand CDG immunological involvement!

Access it **HERE**

This questionnaire is for the entire CDG Community:

- **For patients with and without immunological problems!**

Your participation is crucial!

Help us learn more about CDG, so that targeted and effective clinical guidelines and therapies may be developed! A call for participation among CDG patients and families will be launched soon!

Hope we can count with YOU!

A project created and led by the:

PORTUGUESE ASSOCIATION

Portuguese Association for CDG
www.apcdg.com

In collaboration with the:

CDG & Allies – PPAIN
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Major organs of the immune system (page 11).
https://primaryimmune.org/about-primary-immunodeficiencies/relevant-info/the-immune-system

Cells of the innate and adaptive immune responses (page 12).
Nature Reviews Cancer 4, 11-22.

For further information please contact: Vanessa Ferreira (Volunteer and founder, Portuguese Association for CDG (APCDG), Portugal & CDG Professionals and Patient Associations Working Group, CDG-PPAWG.

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THANK YOU FOR HELPING US!

PORTUGUESE ASSOCIATION

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