Lay Language Summary of the Article "Immunological aspects of congenital disorders of glycosylation (CDG): a review"

Propose title for the lay summary:

Immunological dysfunction in Congenital Disorders of Glycosylation (CDG)

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What is and what does the immune system?

The immune system consists in a network of cells, tissues, and organs that work together to protect the body.

The immune system is responsible for defending our body against microorganisms and unhealthy cells. It also 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.

Examples of dysregulations of the immune system, include:

- 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.
- Allergy – when the immune system recognizes something that is harmless to most people as a threat (for e.g food allergy). Symptoms/signs of allergies include, rashes, trouble breathing, hitch or cough, among others.

How important are sugars (glycans) for the functioning of the immune system?

Sugars play various roles in the immune system. Many of the proteins that form and are produced by the immune system are modified with sugars, so sugars are important in the recognition of threats, 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.

In CDG patients, the mechanism that attaches sugars to proteins and fats is defective, therefore, the immune responses may be inefficient and/or altered.

Take home messages

- At least 10% of all CDG forms have immunological affectations;

- Immunological affectations 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 problems;

- For the wide majority of CDG there are no targeted treatments for immunological affectations;

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

- The extent and importance of immunological affectation in CDG is very likely underestimated and has been overlooked, due to the lack of detailed reports and monitorization of immunological parameters;

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

A thorough analysis of the literature allowed us to identify:

- 13 CDG forms, whose patients present with immunological affectations (currently, there are 133 CDG identified, thus approximately 10% of all CDG have immunological affectation);
- Among those 13 CDG, there are some forms in which the immunological problems are of major importance (they are the predominant or the most severe affectation), 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 affectation

CDG with major immunological affectations	CDG with minor immunological affectations
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

Main signs & symptoms

CDG with major immunological affectations

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 the person's own organs).

MAGT1-CDG: Impaired capacity of 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 the EBV infections. Clinical trials based on these observations are underway.

MOGS-CDG: Increased resistance to infections with enveloped viruses (viruses that are covered in a layer made of proteins and sugar) that are dependent on sugars, 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 lethal).

- When vaccinated, patients failed to respond to some of the vaccines and lost the protection conferred by vaccination very soon after being vaccinated.
- 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 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 showed lack of immune cells.

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

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

- Immunological reports of CDG patients are scarce and not very detailed, what led us to conclude that immunological affectation is 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 defence mechanisms.

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 alteration in CDG can be achieved.