Madalena Romão Parrado
BSc in Molecular Biology and Genetics

ADVANCING THE UNDERSTANDING OF CONGENITAL DISORDERS OF GLYCOSYLATION SYMPTOMS TO ACCELERATE THERAPIES

Dissertation to obtain the master's degree in Biochemistry for Health

Adviser: Paula Videira, Assistant Professor, NOVA School of Science of Technology
Co-adviser: Vanessa Ferreira, Founder and Researcher at CDG&Allies PPAIN; Founder and Operations Leader at World CDG Organization

March 2023

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NOVA School of Science and Technology

March, 2023

Advancing the understanding of Congenital Disorders of Glycosylation symptoms to accelerate therapies

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The work developed during this master project has originated:

Posters:

Falcão M, Parrado M, Pascoal C, Francisco R, Brasil S, Videira PA, Ferreira V. Empowering CDG families and professionals with an arsenal of educational resources. Poster presented at: 2022 Sanford Burnham Prebys Rare Disease Day Symposium & CDG/NGLY1 Family Conference, 2022 Feb 25-27, San Diego, CA, USA (Appendix I)

Alves S, Gomes C, Parrado M, Pascoal C, Ferreira V. A grassroots effort to build community practical tools using the International Clinical Guidelines for the Management of Phosphomannomutase 2-Congenital Disorders of Glycosylation (PMM2-CDG) – A case study transferable across all CDG types. Poster presented at: 2022 Sanford Burnham Prebys Rare Disease Day Symposium & CDG/NGLY1 Family Conference, 2022 Feb 25-27, San Diego, CA, USA (Appendix II)

Oral communications:

Poster presentation at the 2022 Sanford Burnham Prebys Rare Disease Day Symposium & CDG/NGLY1 Family Conference, 2022 Feb 25-27, San Diego, CA, USA

Abstract

Glycosylation plays a pivotal role in numerous cellular processes, having significant implications on human health and illness. Pathologies arising from abnormal glycosylation are termed Congenital Disorders of Glycosylation (CDG). CDG are a growing family of rare genetic metabolic diseases. They are multisystemic disorders and present a wide array of clinical manifestations. Due to CDG'S symptom heterogeneity and rarity, most subtypes don't have a well-defined clinical spectrum and the severity and impact of these symptoms on patients and their families is still unclear. To address these recognizable gaps, we decided to build a patient-centred e-questionnaire aimed at people living with CDG and their family members/caregivers: The CDG Symptom Prioritization Questionnaire (CDGSPQ). Results showed that neurologic & muscular, ophthalmologic and gastrointestinal S&S were considered the most common in CDG patients. Fine and gross motor disabilities and intellectual delay were the most common and the most impactful neurologic manifestations. Strabismus was the most common ophthalmological manifestation, but participants considered it to have a minor impact in the patient's everyday life. Dysphagia was considered both the most persistent and most severe gastrointestinal manifestation. When asked directly which were the most important CDG S&S to treat, patients selected intellectual delay, gross motor disability and seizures. Although it is still a preliminary study, this patient-centred questionnaire is a stepping stone in advancing and expediting CDG research.

Keywords: Glycosylation; congenital disorders of glycosylation; rare diseases; clinical heterogeneity; symptom prioritization; patient-centred study.

Resumo

A glicosilação desempenha um papel fundamental em inúmeros processos celulares, tendo implicações significativas na saúde e doença humana. As patologias decorrentes da glicosilação anormal são denominadas de Doenças Congénitas da Glicosilação (CDG). As CDG são uma família de doenças metabólicas genéticas raras. São distúrbios multissistémicos e apresentam uma grande diversidade de manifestações clínicas. Devido à heterogeneidade dos sintomas das CDG e à sua raridade, a maioria destas doenças não possui um espectro clínico bem definido. Além disso, a gravidade e o impacto dos sintomas das CDG nos pacientes e nas suas famílias ainda não são claros. Para abordar essas lacunas reconhecidas, decidimos construir um questionário eletrónico, centrado no paciente, destinado a pessoas que vivem com CDG e os seus familiares: o Questionário de Priorização de Sintomas das CDG (CDGSPQ). Os resultados mostraram que os sintomas neurológicos e musculares, oftalmológicos e gastrointestinais foram considerados os mais comuns em pacientes com CDG. As deficiências motoras e o atraso intelectual foram as manifestações neurológicas mais comuns e mais impactantes. O estrabismo foi a manifestação oftalmológica mais comum, mas a maior parte dos participantes consideraram que tem um impacto menor na vida do paciente. A disfagia foi considerada a manifestação gastrointestinal mais persistente e mais grave. Quando perguntados diretamente quais eram os sintomas das CDG mais importantes a tratar, os pacientes selecionaram atraso intelectual, deficiência motoras e convulsões. Embora ainda seja um estudo preliminar, este questionário centrado no paciente é um passo importante para avançar e acelerar a pesquisa em CDG.

Termos chave: Glicosilação; distúrbios congénitos de glicosilação; doenças raras; heterogeneidade clínica; priorização de sintomas; estudo centrado nos pacientes.

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List of Abbreviatures

CDG	Congenital Disorders of Glycosylation
CDGSPQ	CDG Symptom Prioritization Questionnaire
S&S	Signs and Symptoms
SLE	Stroke-like episodes
QoL	Quality of Life
GIT	Gastrointestinal

Chapter 1. Introduction

1.1. Congenital Disorders of Glycosylation (CDG) - Inherited genetic defects in glycosylation

Glycosylation is a dynamic cellular process involving the assembly, trimming, and transfer of glycans (also known as sugar trees) onto proteins, lipids or other saccharides to create glycoconjugates.[1]
Glycosylation reactions mainly occur in the endoplasmic reticulum-Golgi pathway through the highly coordinated action of glycosyltransferases and glycosidases.[2,3]
Glycans can be linked and combined in several different ways, creating a variety of structures on lipid and protein molecules. This fact explains the diversity and complexity of glycoconjugates.[4] They have multiple crucial roles in numerous organic processes, such as cellular response to environmental stimuli, cellular growth, differentiation and metabolism as well as structural roles in, on, and outside cells.[1,5]
Considering glycans' important involvement in biological processes, it is unsurprising that an increasing number of diseases are attributed to molecular defects in glycosylation.[6] Congenital disorders of glycosylation (CDG) are an example of disorders directly caused by altered glycosylation.
CDG are inherited metabolic rare diseases containing genetic defects in glycan biosynthesis and metabolism.[7,8] The vast majority of these disorders are inherited in an autosomal recessive manner, but autosomal dominant and X-linked forms have also been described.[9]
CDG are clinically complex conditions since modifications on protein and lipid glycosylation can affect practically all organs/systems. Depending on the altered glycosylation pathway, CDG can be classified into four categories: N-linked glycosylation disorders (most common), O-linked glycosylation disorders, combined N- and O-linked/multiple glycosylation disorders, and lipid and glycosylphosphatidylinositol anchor biosynthesis disorders.[10,11]
More than 150 types of CDG have already been reported and this number is still increasing.[8] The growing number of known CDG and the wide array of CDG signs and symptoms (S&S), which can overlap with many other diseases, pose a serious diagnostic challenge.[12]
Provided that a CDG is clinically suspected, some forms of CDG can be broadly identified with a blood test that looks for abnormal glycan patterns in proteins such as transferrin and apolipoprotein C-III. These initial screening tests help in the identification of the affected glycosylation pathway, but additional tests must be done to identify the specific CDG subtype. For most CDGs, molecular genetic testing is the most accurate method to confirm a CDG diagnosis.[13]
Understanding the particular pathophysiological mechanisms leading to the different phenotypes seen in CDG is essential to achieve better diagnostics, disease management and therapeutic solutions.[14] Unfortunately, our knowledge on the molecular and cellular mechanisms driving CDG pathogenesis remains limited.[15] Therefore, it is unsurprising that most CDG still lack targeted and effective treatments. Currently, the therapy options, which are available for some CDG types, are mainly restricted to symptom-management approaches, monosaccharide supplementation, and repurposed drugs.[16]

1.2. CDG symptoms and their diversity

CDG are known for including 'nearly' all types of signs and symptoms.[17]

Since glycosylation is essential to many cellular processes, CDG present a broad variety of clinical manifestations, potentially affecting multiple organs/systems.[18]

CDG's signs can vary considerably, both within and between types. Symptom severity can also be rather disparate, even among individuals with the same type of CDG, ranging from mild to severe, disabling or life-threatening.[19,20]

Most clinical manifestations begin during infancy, but the onset of symptoms can also occur in adulthood for some CDG types.[21]

CDG typically present significant neurological abnormalities accompanied by variable dysfunction of other organs and systems, as well as developmental delays, failure to thrive, and dysmorphic features.[14,19]

The most frequently observed neurological S&S in these disorders are intellectual disability, seizures, hypotonia, fine and gross motor disability, myopathies, neuropathies, stroke-like episodes and behavioral disturbances.[19]

The other frequently affected organs and systems include the eyes, gastrointestinal tract, heart, liver, muscles, skeleton, skin, and the immune system.[14]

Many patients present dysmorphic features, such as facial dysmorphia, inverted nipples, abnormal fat distribution and/or strabismus, which can help the recognition of CDG in early stages of the disease.

Due to the rarity and symptom heterogeneity of CDG, compiling a complete list of signs affecting each subtype is still a challenge. In fact, the majority of CDG lack a clearly defined clinical spectrum.[19]

The management of CDG symptoms is dependent on several factors such as the specific CDG type, the affected body systems, age, and other existing health conditions. Naturally, the impact of CDG on patients and their families is difficult to access, as it can vary significantly.[21,22]

1.3. People-centred research in CDG

Overcoming the limited understanding of CDG's biological and clinical aspects is essential to expedite research and therapy development, improve symptom management and ultimately ensure that patients receive the best possible care.[14] Thus, it is important to invest in a meticulous description of the clinical manifestations, disease course, clinical outcomes and disease impact in patients' daily life.[23]

Since patients and their family members experience the disease on a daily-basis and are continuously seeking detailed medical information regarding their disorders, they are distinctively well-positioned to provide input on CDG health-related topics. Collaborating with them and attentively considering their perspectives is, therefore, of the most importance.[24]

In fact, people-centricity methodologies have been gaining ground in biomedical research, especially in studies regarding chronic and metabolic diseases.[25]

Literally meaning ‘people at the centre’, people-centricity in research refers to the continued involvement of patients, their family members and/or citizens (lay public) as active partners through the entire research process.[26] The participants of people-centred studies are regarded as equal partners and their unmet needs, hopes, concerns and priorities are continuously sought out and incorporated into the research projects.[27]

People-centricity methods offer efficient tools for participant data collection, such as electronic (e-) questionnaires.[28] The use of web-based platforms is especially beneficial in rare diseases since it helps to overcome patient geographic dispersion, facilitation access to and the inclusion of more participants.[29]

People-centric research can focus on multiple health-related topics, including health-related quality of life and symptom treatment prioritization. Symptom prioritization is essential in biomedical research, particularly in diseases with a great variety of clinical manifestations, such as CDG. It helps identifying the most urgent and critical issues that need to be addressed so that researchers and healthcare providers can direct their efforts and resources on managing and/or treating the most impactful symptoms on the patient's quality of life and overall health.[30]

Ultimately, people-centricity directs biomedical research according to the patients’ and families’ needs, which improves the patient's outcomes and well-being.

1.4. Study Rationale and Aims

CDG’s biological complexity, S&S heterogeneity and rarity make it challenging to define a complete clinical spectrum and to fully understand the severity and burden of these symptoms between patients and their families. To tackle these issues, we decided to build a thorough patient-centred e-questionnaire aimed at people living with CDG and their family members/caregivers: the CDG Symptom Prioritization Questionnaire (CDGSPQ).

The aims of this thesis were:

1. To explore the phenotypic variability of signs and symptoms (S&S) in CDG;
2. To determine the most important CDG clinical manifestations in need of treatment or symptom management, according to the CDG patients and their family members/caregivers;
3. To evaluate the severity and impact of CDG signs on individuals living with CDG and their families/caregivers;
4. To analyse the sociodemographic information of the CDGSPQ participants and CDG patients they represent.

Chapter 2. Materials and Methods

CDG Symptom Prioritization Questionnaire (CDGSPQ)

The CDGSPQ was approved by the ethical committee of the Faculty of Psychology of the University of Lisbon on 24/09/2020. (see Appendix III) E-informed consent was obtained from all the participants.

2.1. Idea/Conceptualization - Motivation for creation of the e-questionnaire

The need to explore the phenotypic variability of S&S in CDG, a knowledge gap long identified by the community, and the necessity of expediting and directing the development of new or improved therapies for these diseases propelled the creation of a patient preference e-questionnaire focused on CDG symptom prioritization.

2.2. Development

2.2.1. Assembling of advisory committees

The scientific/clinical content and structural organization of the questionnaire was established with the support of two advisory committees: one acting as the medical/scientific board and a CDG family/caregivers advisory board to ensure the patient-centeredness of the study. The medical/scientific board was composed of nine persons and the CDG family/caregivers advisory board was composed of four persons.

2.2.2. Selection of impactful CDG S&S to inquire in the questionnaire

The disease manifestations to inquire about in the CDGSPQ were selected according to the results of the PMM2-CDG QoL Questionnaire pilot survey that was previously administered to 23 CDG families and 19 clinicians in the 4th World CDG Conference.[31]

The 7 most impactful symptoms for each age group represented in the QoL survey (infancy, childhood, adolescence, adulthood) were collected and analysed by the medical and patient advisory boards. After the committees' feedback, 18 manifestations were selected to inquire about: kyphosis/scoliosis, hypotonia, food allergies, behaviour problems, development delay, dysarthria, gastrointestinal problems, liver problems, infections, ataxia, seizures, stroke-like episodes, osteopenia, coagulopathy, puberty issues, sleep problems, ophthalmological problems and neuropathy.

2.2.3. Identification of articles and questionnaires for adaptation to CDGSPQ

In addition to identifying the most impactful CDG symptoms, literature research on healthcare and management strategies was conducted, using PubMed.

The combinations of keywords selected concerned diet and management/rehabilitation strategies in CDG and on other rare diseases with similar S&S. The list of keyword combinations and search results

(Supplementary Table 7.1) and the inclusion and exclusion criteria applied (Supplementary Table 7.2) are displayed in Appendix IV.

The initial paper screening step was based on title and abstract. Reviews and non-English language articles were excluded, as were the duplicates, using the Mendeley duplicate removal tool.

The remaining articles/surveys were screened by reading the full body text. Those that did not concern CDG or other rare diseases with the same manifestations were excluded, as well as any CDG dietary strategies and food supplementation articles with unknown CDG type. Articles regarding animal models were also considered when containing relevant dietary strategies to implement in humans.

18 articles and 3 surveys were selected as the basis for the development of the CDGSPQ.

Figure 2.1 summarizes the article selection process, which was carried out by one independent researcher.

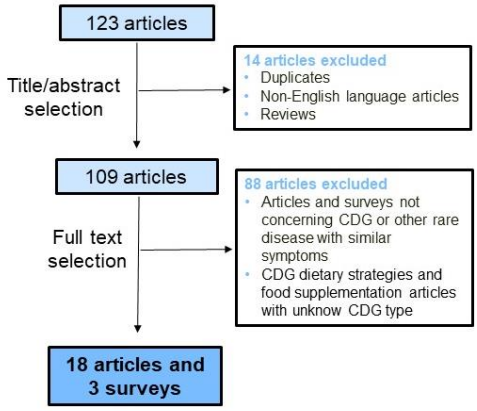

Figure 2.1. Schematic representation of the literature research on healthcare and management strategies and the applied exclusion criteria. The initial paper screening (based on title and abstract reading) resulted in the exclusion of 14 articles (duplicates, reviews, and articles not in English). The second paper screening (based on full article reading) resulted in the exclusion of 88 articles. Amongst these were articles and surveys not related to CDG or other diseases with similar symptoms and dietary and food supplementation articles with unknown CDG type. 18 articles and 3 surveys were selected as the basis for the CDGSPQ.

2.2.4. Definition of the target audience

Given the patient preference exploratory nature of the study, people living with CDG and their family/caregivers were defined as the CDGSPQ target audience. Family/caregivers of CDG people who passed away were also included in the study.

2.2.5. Construction of the questionnaire and glossaries

The written content of the CDGSPQ was based on the articles and surveys selected in the literature research and structured according to the most impactful CDG symptoms chosen from the QoL questionnaire.

The survey employed different question types such as multiple choice, matrix, classification scales, and open-ended questions.

To ensure the reliability and accuracy of the collected data, the survey was developed in a lay friendly language, so all participants could clearly understand its content. Five thematic glossaries were also prepared and disseminated within the participants to clarify the terminology used: one regarding signs and symptoms, one about available treatments, one on diet options, one on management and rehabilitation therapies and one on the health care specialities involved in CDG.

2.2.6. Questionnaire Structure

The CDGSPQ comprises two parts. Part 1 has the following sections: Participant relationship with CDG & sociodemographic information and CDG signs & symptoms (S&S). Part 2 addresses General CDG care & management symptom (including medication, food supplements, management/rehabilitation approaches, hospitalizations, healthcare specialists and reference centers and services), Impact of CDG S&S on the caregiver's activities tasks and Health literacy assessment. Three questions were added to the end of the questionnaire to evaluate its understandability, the use and usefulness of the glossaries provided, and to assess the experience of participants (Health literacy assessment section). The present dissertation only incorporated the information collected from Part 1 of the survey.
Figure 2.2 displays the structure of the CDGSPQ.

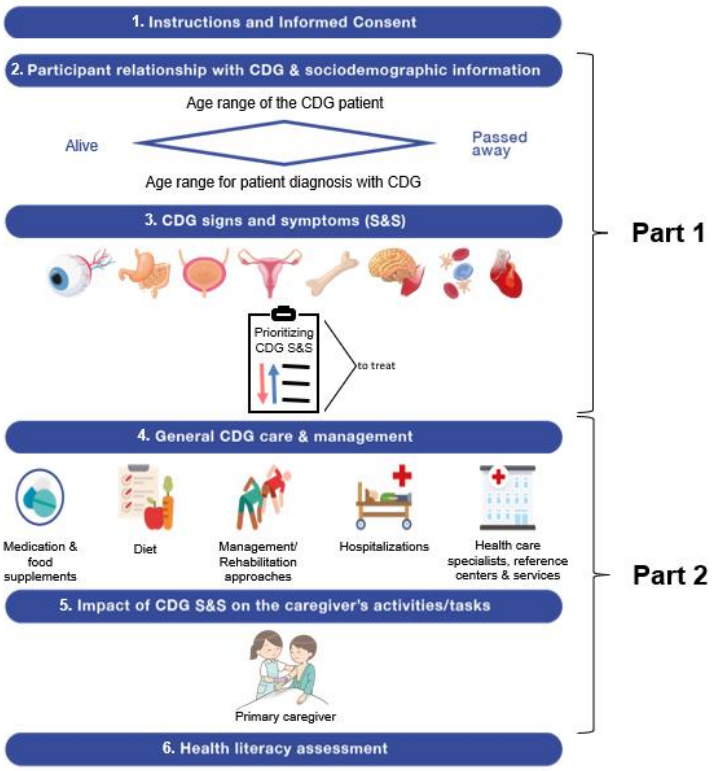

Figure 2.2. Schematic representation of the structure of the CDGSPQ. Part 1 comprises the participant relationship with CDG & sociodemographic information and CDG signs & symptoms (S&S) sections and Part 2 addresses the general CDG care & management symptom, the impact of CDG S&S on the caregiver's activities tasks and the health literacy assessment sections.

2.2.7. CDGSPQ implementation using the SurveyMonkey software

Taking advantage of the methodology already implemented by the CDG & Allies PPAIN[32]. Survey Monkey was the chosen platform to implement the e-questionnaire (http://www.surveymonkey.net - Copyright #1999–2019 SurveyMonkey). To assure participant anonymity and avoid duplication of results, the participants' IP identifier was not recorded and multiple entries from the same device were not permitted.

The cloud-based platform allowed the construction of a survey with different question types and the addition of logic to the questions.

Despite the total number of items in the survey being 82, the conditional logic structuring influences the number of questions the participants have to answer, depending on the participant type (CDG patients or caregivers will answer a maximum of 77 questions; caregivers of a deceased patient who lived with PMM2-CDG will answer a maximum of 81 questions).

2.3. Revision, piloting, and translation

2.3.1. Validation of the questionnaire by CDG families and expert clinicians/researchers

The professional advisory committee, composed of 4 persons, the patient advisory committees, composed of 4 persons, 5 members of the CDG & Allies PPAIN and a team of 5 volunteers reviewed the content of the glossaries as well as the questionnaire, its structure, language appropriateness and were responsible for the survey piloting.

2.3.2. Number of multilingual versions available for the questionnaire:

Anticipating the global outreach of the study, the questionnaires were translated into six additional languages: French, Spanish, Portuguese, Italian, Dutch and German. Translations were performed by native speakers and reviewed by medical/biomedical experts.

2.4. Preliminary Engagement Phase

2.4.1. Description of the pre-launch campaign

Prior to the launch and active recruitment campaigns, a social media-based campaign was set-up during the month of December 2021. Informative posts and publications on the project and on the important role of patient input in CDG research were prepared and disseminated on social media networks and via e-mailing to incite patient recruitment.

2.5. Survey Launch, recruitment and result dissemination

The survey was launched on the World CDG Organization website [33] in 2021, initially for one month (March-April) and relaunched in 2022 for five months (January-May).

The dissemination of the survey and participant recruitment were highly dynamic processes. They comprised social media engagement, through the publication of motivational posts and questions from the survey, recruitment via emailing and newsletter within the CDG community and on CDG events.
After the closing of the questionnaire, thank you posts and e-mail messages were shared.
The last engagement phase was focused on result communication: survey results were distributed and communicated at several events, platforms and using various formats targeting the different audiences (scientists, clinicians, CDG patients, family members and society).

2.6. Statistical analysis

CDGSPQ responses were directly exported from SurveyMonkey to Microsoft Excel (2303).
Given the scientific/medical and structural construction of the CDGSPQ, and thanks to the targeted dissemination strategy developed, “random” participation of non-CDG patients/family caregivers was considered highly unlikely.
Patients without a confirmed CDG diagnosis were excluded. Possible patient duplications were carefully screened and when in doubt both reports were excluded. All participants failing to complete all relevant sections were eliminated from further analysis.
Descriptive statistics were used to analyse and report the data.

Chapter 3. Results

CDG Symptom Prioritization Questionnaire

The CDG Symptom Prioritization Questionnaire (CDGSPQ) was created to help characterizing CDG's diverse array of S&S and their impact on the patient and family members' lives, as well as to determine the most important signs in need of treatment and better management.

This survey was available on the World CDG Organization website[33], initially for one month (March-April, 2021) and later, in 2022, for five months, until May 3rd.

During the initial launch of the questionnaire, from March until April of 2021, 65 responses were received worldwide.

On average, these participants completed the survey in 45 min.

As previously stated, the present dissertation focuses on the information collected from the first part of the survey, concerning CDG signs & symptoms.

Following a brief characterization of the survey's respondents and CDG patients, the results regarding CDG S&S will be presented.

3.1. Participant relationship with CDG and sociodemographic information

3.1.1. Geographical distribution of the sample

As observed in Figure 3.1, survey respondents included people from 22 different nationalities. The Brazilian, American, Australian, French and Portuguese nationalities were the most represented within the survey's respondents.

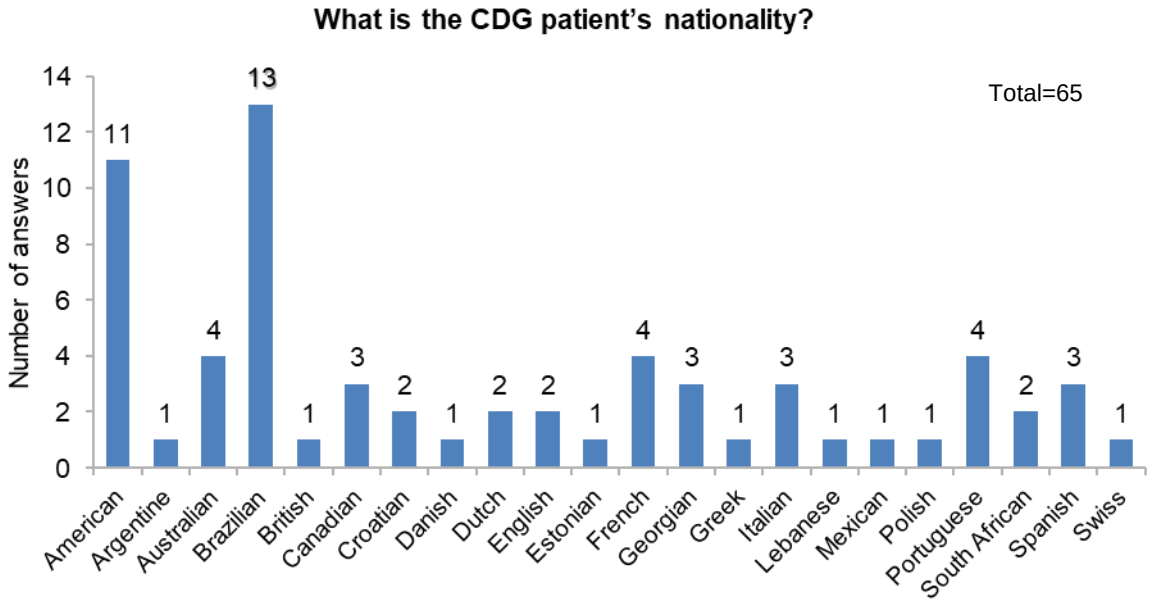

Figure 3.1. Geographical dispersion of the survey's respondents. Geographical dispersion of the survey's respondents. 22 different nationalities were represented in the survey's sample, being the Brazilian and American the most represented.

3.1.2. Respondents' status

As seen in Fig.4, most of the participants completing the CDGSPQ were parents, mainly mothers of people living with CDG (82%, n = 53/65). Only a few of the respondents were either grandparents or uncles/aunts of the CDG patient Additionally, two respondents shared that they were living with CDG.

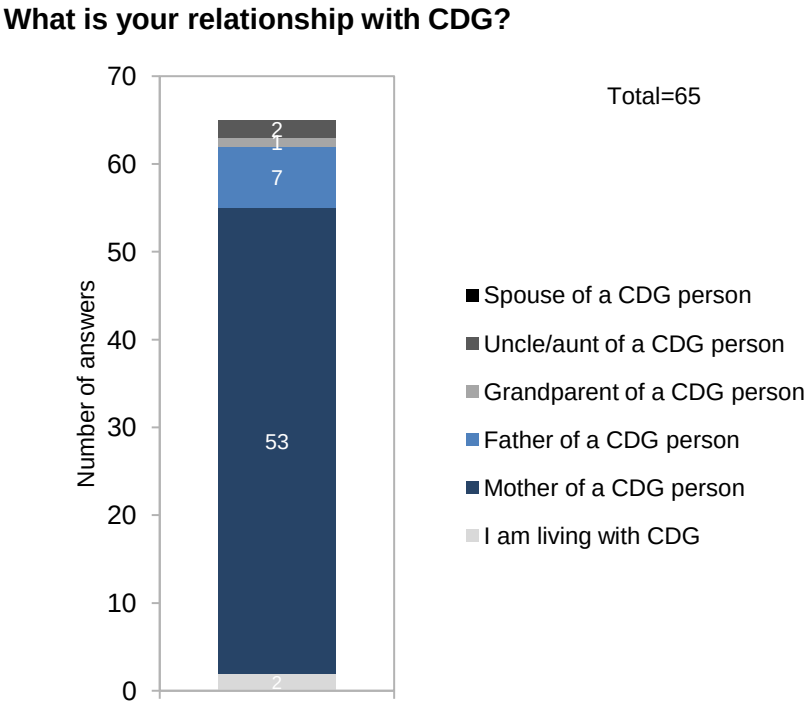

Figure 3.2. Respondent status. Most respondents were the parents of people living with CDG. 82% (n = 53/65) were the mothers of CDG patients. A minimal number of respondents were grandparents or uncles/aunts of the CDG patient. Also, two participants mentioned they were living with CDG**.**

3.1.3. Age Range of CDG Patients

The results showed that most CDG patients disclosed in the survey were of young age, being the most common age range between 2 and 11 years old (51%, n = 33/65), followed by 0-24 months (18%, n = 12/65), as seen in Figure 3.3.

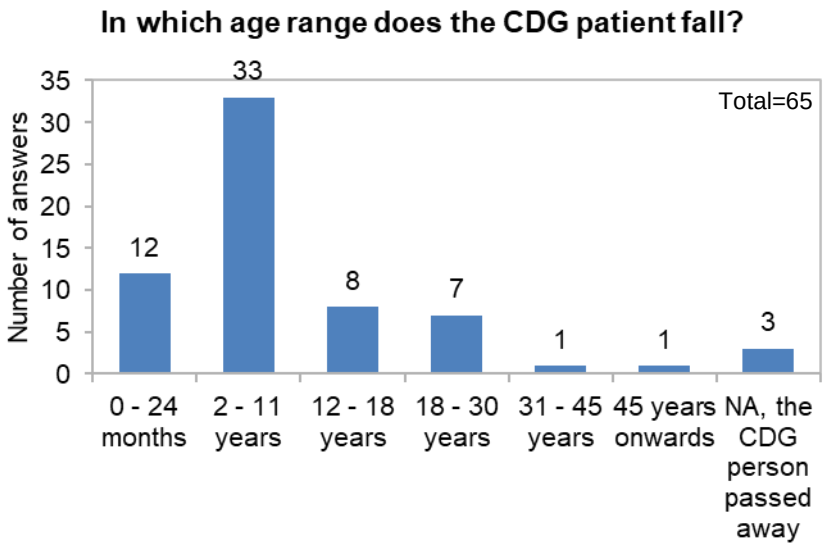

Figure 3.3. Age range of CDG patients disclosed in the survey. The most common age range within the CDG patients was 2-11 years old (51%, n = 33/65), followed by 0-24 months (18%, n = 12/65).

3.1.4. Gender of the CDG Patients

Regarding the gender of the CDG patients (Figure 3.4), the male proportion of patients (63%, n = 41/65) was high compared to the female proportion (37%, n = 24/65).

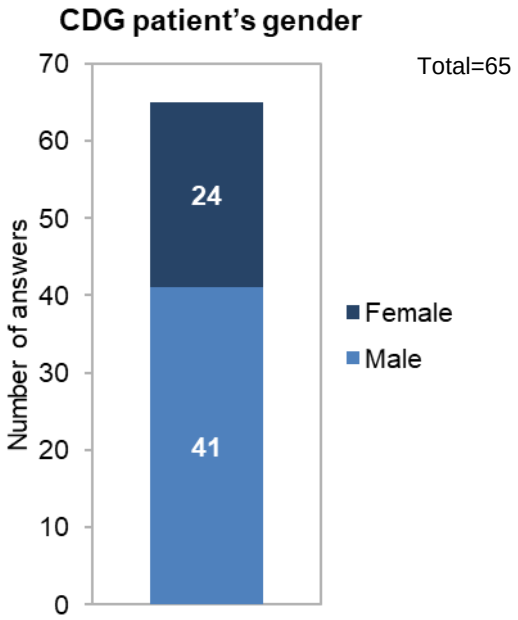

Figure 3.4 Gender of the CDG patients disclosed in the survey. The majority of the CDG patients were male (63%, n = 41/65).

3.2. CDG signs & symptoms

Since CDG are multisystemic, participants were inquired about the different systems/organs that can be affected in the disease. The respondents were presented with different types of signs & symptoms (S&S) observed in CDG (ophthalmologic S&S, gastrointestinal S&S, bladder S&S, reproductive S&S, skeletal S&S, neurologic and muscular S&S and haematological & immunological S&S) and were asked to select the ones that the person living with CDG exhibited.

As seen in Figure 3.5, neurologic & muscular S&S were considered the most common in CDG patients (91%, n = 59/65). A substantial number of participants also regarded ophthalmologic and gastrointestinal manifestations to be very common amongst the CDG patients (71%, n = 46/65, 52%, n = 34/65 respectively). A less significant number of participants shared the presence of skeletal and haematological & immunological S&S (46%, n = 30/65, 37%, n = 24/65 respectively) in the CDG patients. A fair share of the participants chose the option "Other" (45%, n = 29/65) which included manifestations unrelated to a specific organ/system (unexplained fever episodes, insomnia, shortness of breath, fluid retention, fatigue, pain and/or elevated ALT and/or AST). A minor number of respondents shared the presence of bladder and reproductive S&S in the CDG patients (17%, n = 11/65, 14%, n = 9/65 respectively).

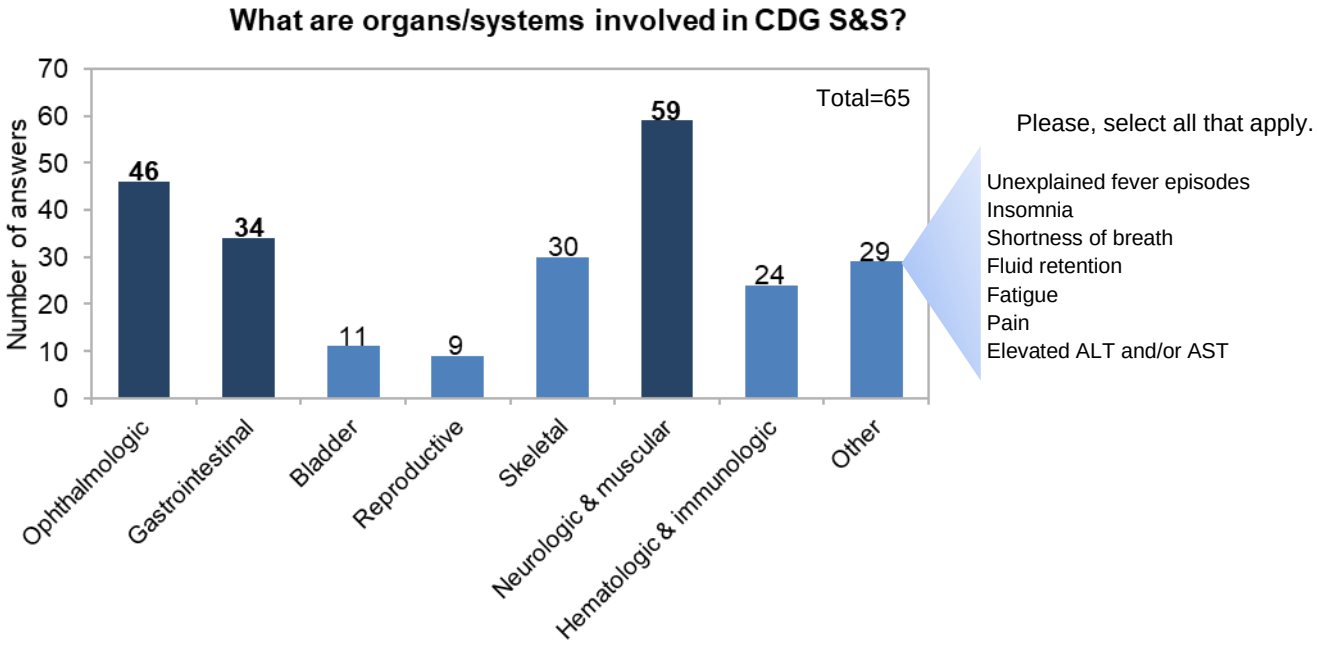

Figure 3.5. CDG signs and symptoms of people living with CDG per organ/system affected. The survey's participants appointed neurologic and muscular S&S (91%, n = 59/65) as the most common manifestations in CDG patients, followed by ophthalmologic (71%, n = 46/65) and gastrointestinal S&S (52%, n = 34/65). Less than half of the participants shared the presence of skeletal and haematological & immunological S&S (46%, n = 30/65, 37%, n = 24/65 respectively). Bladder and reproductive S&S seemed to be the less common manifestations in the CDG patients (17%, n = 11/65, 14%, n = 9/65 respectively). A fair share of the participants chose the option "Other" (45%, n = 29/65), which included manifestations without a specific organ/system associated, such as unexplained fever episodes, insomnia, shortness of breath, fluid retention, fatigue, pain and/or elevated ALT and/or AST.

The following results will focus on the systems the survey participants considered most significant in CDG (neurologic and muscular manifestations, ophthalmologic and gastrointestinal manifestations) and provide a thorough symptoms/signs assessment.

3.3. Neurologic & Muscular S&S

Most individuals affected with CDG present neurologic and muscular abnormalities.[34]

To better understand the effect of neurological S&S in the CDG, the participants of the survey were given some examples of neurological manifestations reported in CDG (intellectual delay, social problems, fine and gross motor disabilities and/or speech problems) and were asked to describe the severity and impact of the signs the patient presented. (Fig. 3.6)

Regarding their prevalence, all manifestations seemed to be very common in the survey's CDG patients. Fine and gross motor disabilities and intellectual delay were reported as the most frequent amongst the patients (97%, n = 57/59; 88%, n=52/59 and 88%, n=52/59 respectively). A substantial number of participants also considered speech and social problems to be very common (83%, n = 49/59; 68%, n=40/59 respectively).

In terms of symptom severity, the participants reported gross motor disability (69%, n = 36/52), intellectual delay (65%, n = 34/52) and speech problems (63%, n = 31/49) as the most severe. The remaining manifestations, social problems and fine motor disabilities, were also considered very severe by the majority of respondents (58%, n = 23/40; 53%, n = 30/57 respectively).

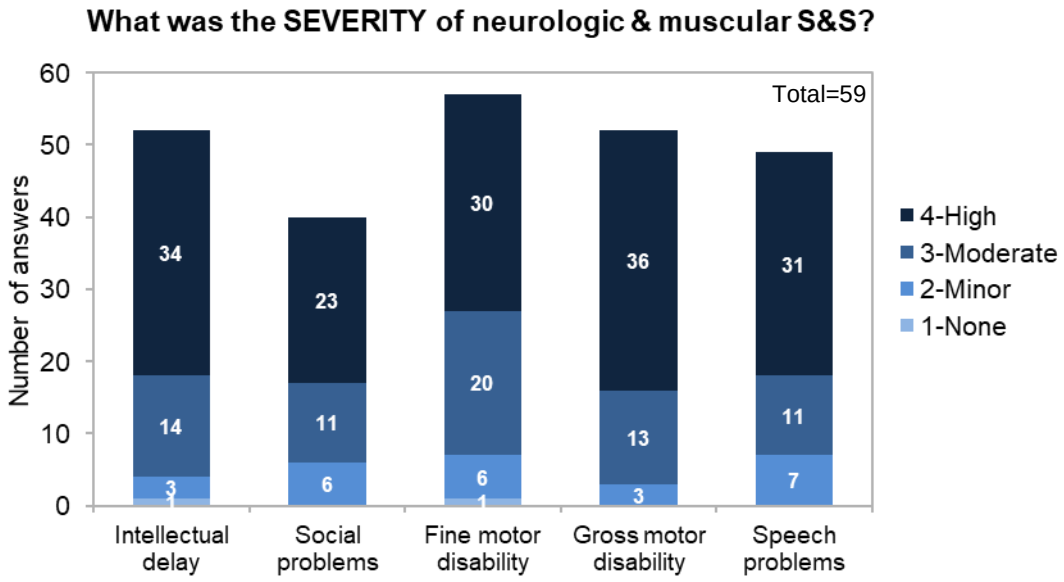

Figure 3.6. Neurological & muscular CDG manifestations' prevalence and their severity according to the survey respondents. The respondents considered fine and gross motor disabilities and intellectual delay as the most common neurologic & muscular S&S in CDG patients (97%, n = 57/59; 88%, n=52/59 and 88%, n=52/59 respectively). Speech and social problems also seemed to be very common in the CDG patients (83%, n = 49/59; 68%, n=40/59 respectively). Regarding disease severity, the participants regarded gross motor disability (69%, n = 36/52), intellectual delay (65%, n = 34/52) and speech problems (63%, n = 31/49) as the most severe neurologic & muscular manifestations. Social problems and fine motor disabilities were considered very severe as well (58%, n = 23/40, 53% n = 30/57 respectively).

When it comes to the impact of neurologic & muscular S&S, all manifestations appeared to be very impactful on the CDG patient's everyday life, as seen in Figure 3.7. The respondents considered gross motor disability (75%, n=39/52), intellectual delay (73%, n=38/52) and speech problems (65%, n=32/49) as the most impactful. Social problems and fine motor disability also had a high impact on the patients' life (60%, n=24/40; 58%, n=33/57 respectively).

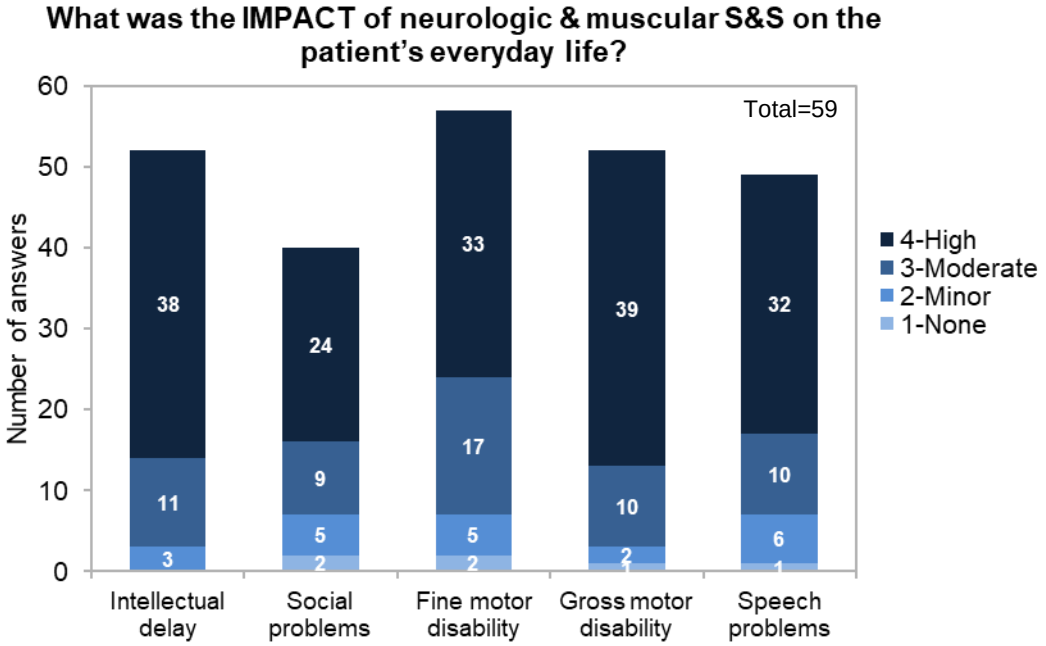

Figure 3.7. Impact of the neurological & muscular CDG manifestations on the CDG patient's everyday life. Participants appointed gross motor disability (75%, n=39/52), intellectual delay (73%, n=38/52) and speech problems (65%, n=32/49) as the most impactful manifestations on CDG patient's everyday life. Additionally, social problems and fine motor disability also seemed to have a high impact on the patient's day-to-day (60%, n=24/40; 58%, n=33/57 respectively).

3.3.1. Seizures

The causes of seizures in CDG are still uncertain and accurate semiology descriptions are still lacking.[35] Therefore, a specific survey section was dedicated to this symptom.

First, the survey respondents were inquired about the occurrence of seizures in the CDG patient. Almost half of the participants (47%, n = 28/59) reported the occurrence of this manifestation throughout the patient's life.
Second, they were inquired about the frequency of the seizures the patient had suffered (Figure 3.8A). Respondents shared that they mostly happened between 1-3 times per year, whether the awareness was intact or affected (32%, n=6/19). Although, there was also a significant number of participants who shared that they experienced them several times a day, from 1 till 10 per day (26%, n=5/19). When asked about the level of awareness/consciousness of the patient, seizures with impaired awareness were as common as seizures without impaired awareness (68%, n=19/28). Concerning seizures with awareness unknown (e.g., seizures that only occur during sleep), participants though they mostly happened 4-11 times per year or 1-6 per week (27%, n=3/11 for both).
Third, the respondents were inquired about the impact that seizures have in the CDG patient's everyday life (Figure 3.8B). Independently if they were or not aware, most participants considered that these episodes have a moderate or high impact in the patient's life (74%, n=14/19; 68%, n=13/19).

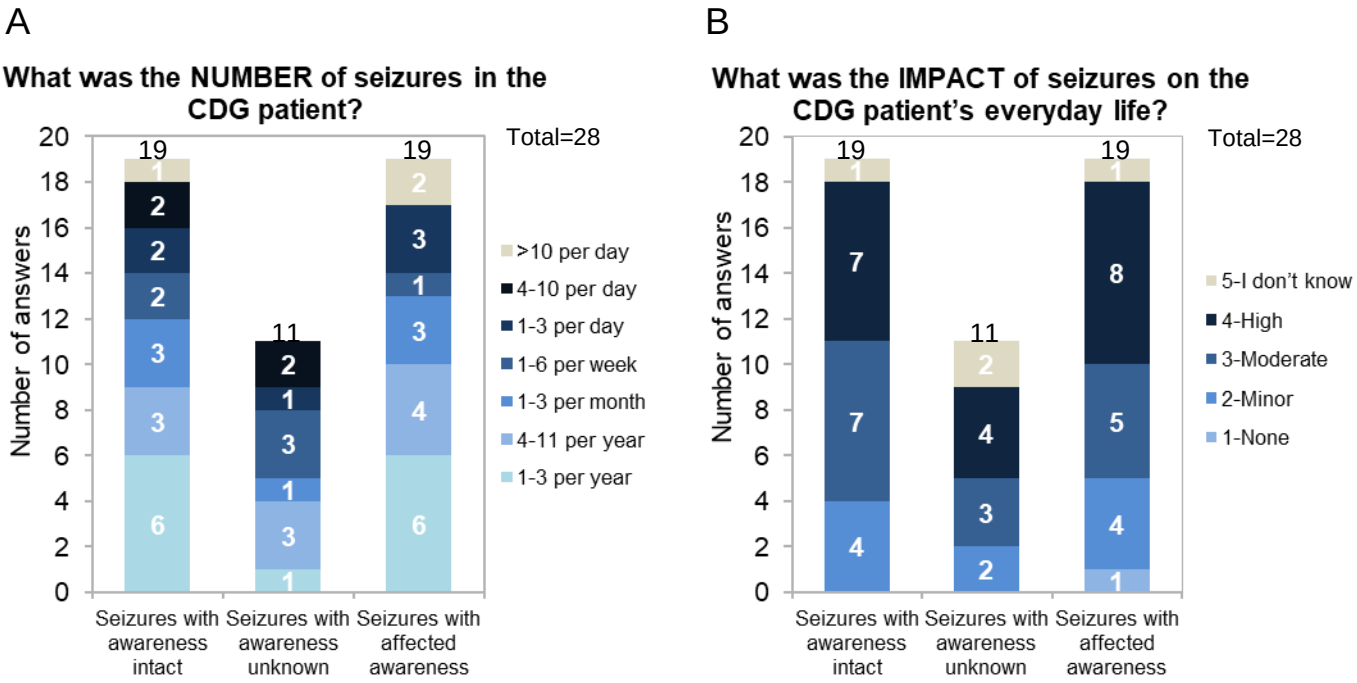

Figure 3.8 A) Frequency of seizures according to the patient's level of awareness of the seizure. Half of the participants (47%, n = 28/59) reported the occurrence of seizures throughout the patient's life. They shared that most patients had 1 to 3 seizures per year (32%, n=6/19) and that seizures with impaired awareness seemed to be as common as seizures without impaired awareness (68%, n=19/28 for both types). A significant number of participants also shared the occurrence of seizures several times a day, from 1 till 10 per day, regardless the seizure's level of awareness (26%, n=5/19). **B) Impact of seizures on the CDG patient's everyday life according to the patient's level of awareness of the seizure.** Most participants considered seizures to have a moderate or high impact in the CDG patient's everyday life, despite the seizure's level of awareness (74%, n=14/19; 68%, n=13/19).

Participants were also inquired about the various causes/triggers of seizures in people living with CDG. Various examples were presented, and the respondents selected those that most applied to their situation/experience (Figure 3.9). They appointed episodes of illness/fever as the most common trigger of seizures in the CDG patients (79%, n=22/28). Less significantly, seizures could also be triggered by tiredness/sleep deprivation (43%, n=12/28), stress (29%, n=8/28) or noise (21%, n=6/28).

A minor share of the participants chose 'Not eating well, low blood sugar' or 'Flashing bright lights or patterns' as triggers (14%, n=4/28).

Additionally, some participants chose the option 'Other' and entered some manifestations not included in the set, like pain or lightness (18%, n=5/28).

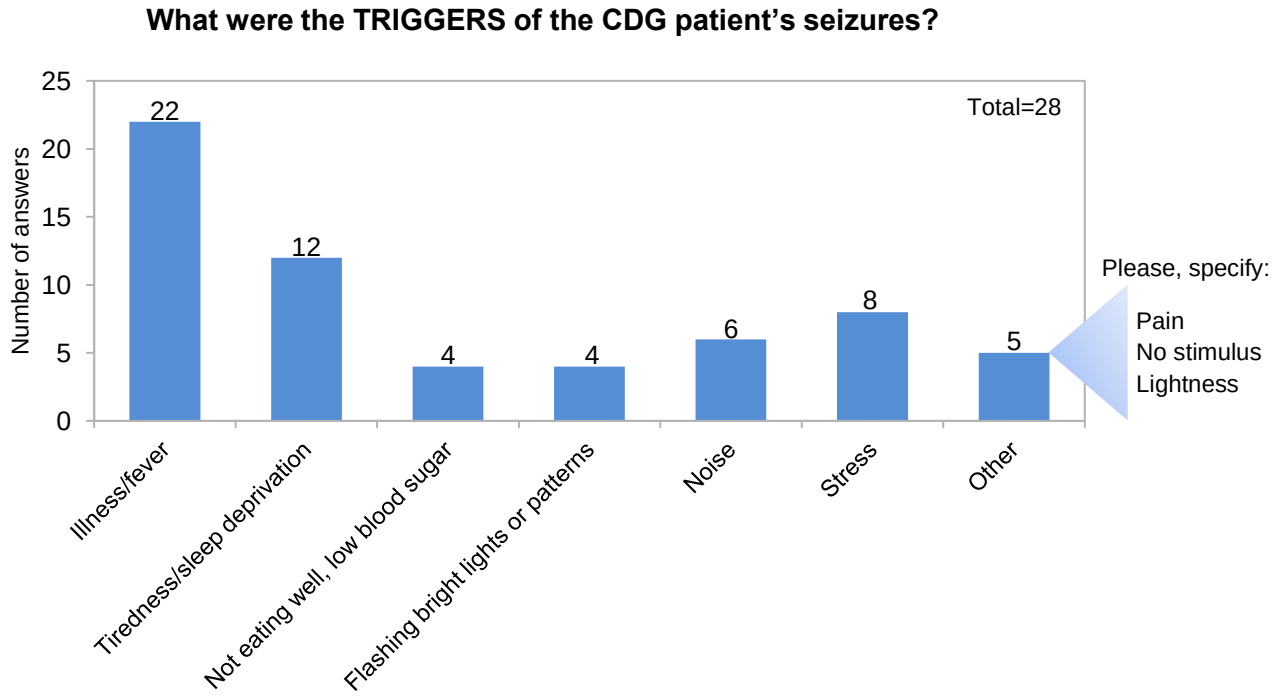

Figure 3.9. Triggers of the CDG patient's seizures. The majority of respondents regarded illness/fever as a recurring trigger for the patient's seizures (79%, n=22/28). Infrequently, tiredness/sleep deprivation, (43%, n=12/28) stress (29%, n=8/28) and noise (21%, n=6/28) also caused seizures in the CDG patients. Very few participants appointed 'Not eating well, low blood sugar' or 'Flashing bright lights or patterns' as triggers (14%, n=4/28). Furthermore, some participants chose the option 'Other' and wrote down signs that were not included in the set, like pain or lightness (18%, n=5/28).

3.3.2. Stroke-Like Episodes (SLE)

The risk factors and clinical features of SLE in CDG are still unknown.[36] Therefore, it seemed essential to ask the participants to describe their experience with the symptom.

Out of the 59 respondents that reported neurological & muscular signs, only 10 (17%, n=10/59) experienced stroke-like episodes. They were asked to share the number of SLE the patient had suffered and to evaluate their impact. (Figure 3.10)

Regarding the number of episodes, most participants shared that the patients had gone through 1 to 3 SLE throughout their life (70%, n=7/10). Only 2 participants reported a number of episodes between 4-6 and 7-9 (20%, n=2/10).

When it comes to the impact of SLE, half of the respondents considered them to have a high impact on the patient's everyday life (50%, n=5/10). A less significant number of participants considered SLE to have a moderate impact in the daily life of the person living with CDG (30%, n=3/10). Few participants considered that they had no impact in the patient's life (20%, n=2/10).

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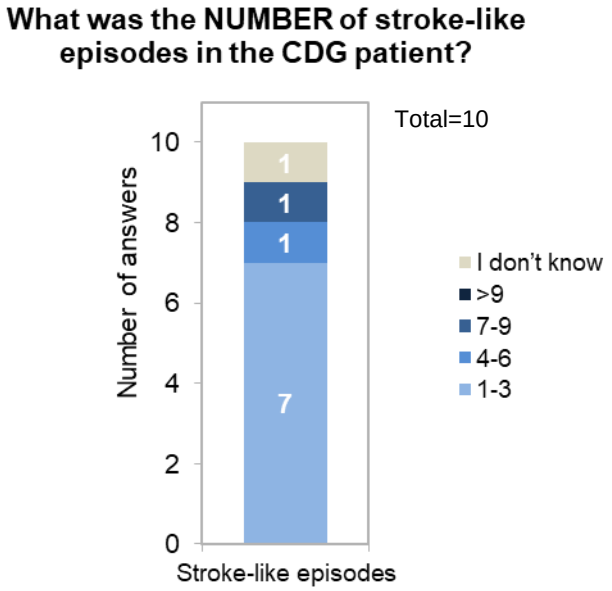

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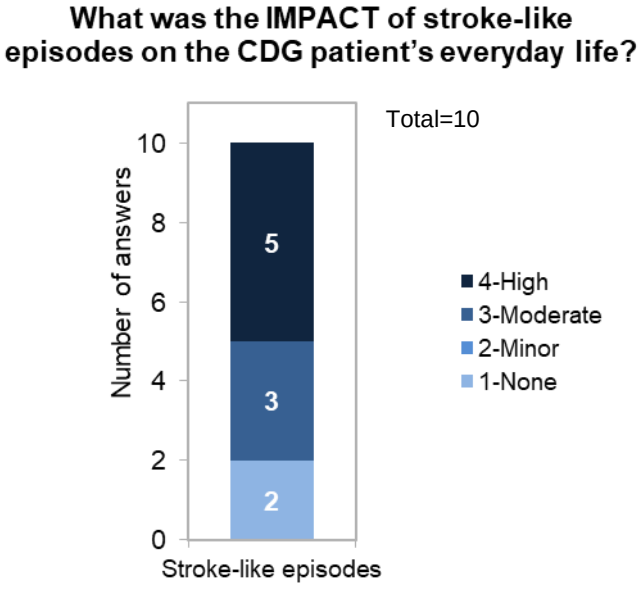

Figure 3.10 A) Number of the patient's stroke-like episodes. The majority of respondents shared that the patients had gone through 1-3 episodes during their lifetime (70%, n=7/10) Only 2 participants shared the occurrence of 4-6 or 7-9 SLE throughout the patient's life (20%, n=2/10). **B) Impact of stroke-like episodes on the patient's everyday life.** Half of the participants stated that SLE had a high impact in the patient's everyday life (50%, n=5/10). Also, a few number of participants considered such episodes to only have a moderate impact in the day-to-day of the patient (30%, n=3/10). Some participants considered that they had no impact in the patient's life (20%, n=2/10).

The survey respondents were also requested to appoint what seemed to have triggered the stroke-like episodes the patients had experienced. As seen in Figure 3.11, illness/fever, infections, and head trauma were the most common triggers selected by the respondents (20%, n=2/10 for each). A less significant number of participants opted to write the specific triggers related to their personal experience (Other): high headaches, migraines, venous thrombosis, and subdural hematoma.

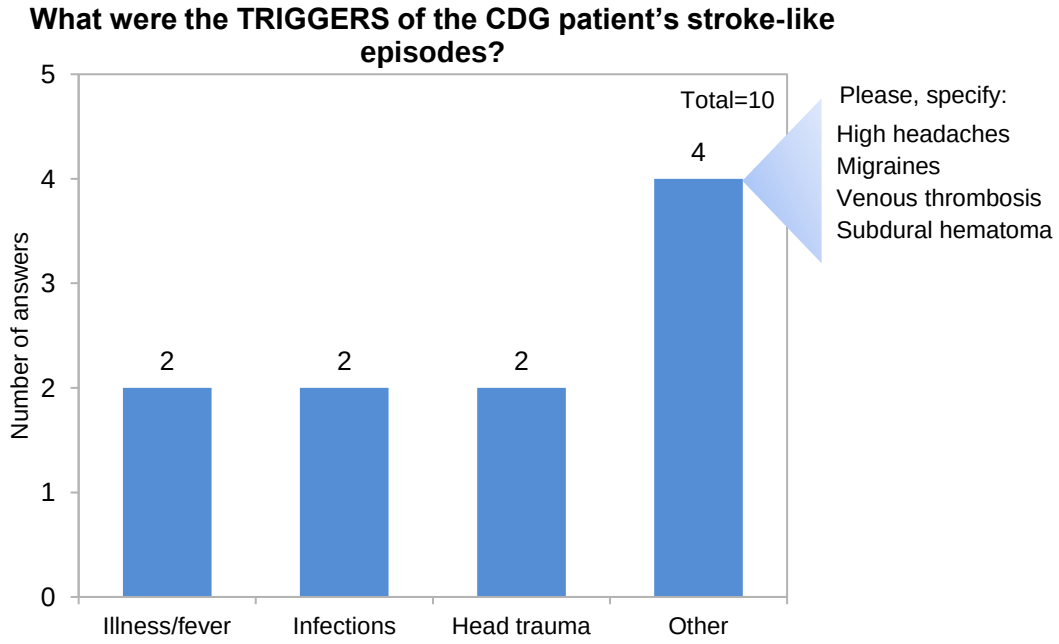

Figure 3.11. Triggers of the patient's stroke-like episodes. Respondents appointed illness/fever, infections and head trauma as the most common triggers of the SLE patients experienced (20%, n=2/10 for each). The remaining 4 participants chose other and wrote the specific triggers related to their personal experience: high headaches, migraines, venous thrombosis and subdural hematoma.

Additionally, the participants were asked to share the initial clinical presentations that suggested the patient was having a stroke-like episode. (Figure 3.12)

Among the suggested manifestations, somnolence was the most common presentation mentioned by the CDG family members/caregivers (70%, n=7/10). Lack of energy & enthusiasm (50%, n=5/10), epileptic seizures (50%, n=5/10) were also appointed as common SLE initial presentations. Less frequently, respondents reported irritability (40%, n=4/10), slurred or slow speech (40%, n=4/10), difficulty in expressing, speaking and understanding (30%, n=3/10) and paralysis of a single limb (30%, n=3/10) as initial SLE manifestations. A minor number of participants selected vomiting, inability to comprehend or formulate language and paralysis of half of the body as initial presentations (20%, n=2/10; 20%, n=2/10; 10%, n=1/10 respectively). Additionally, some participants chose the option 'Other' (40%, n=4/10) and entered specific manifestations related to their experience: dizziness, muscle tightness, numbness/tingling, chest tightness, headaches, mouth and lips dropping, uncontrollable dribbling and/or tears.

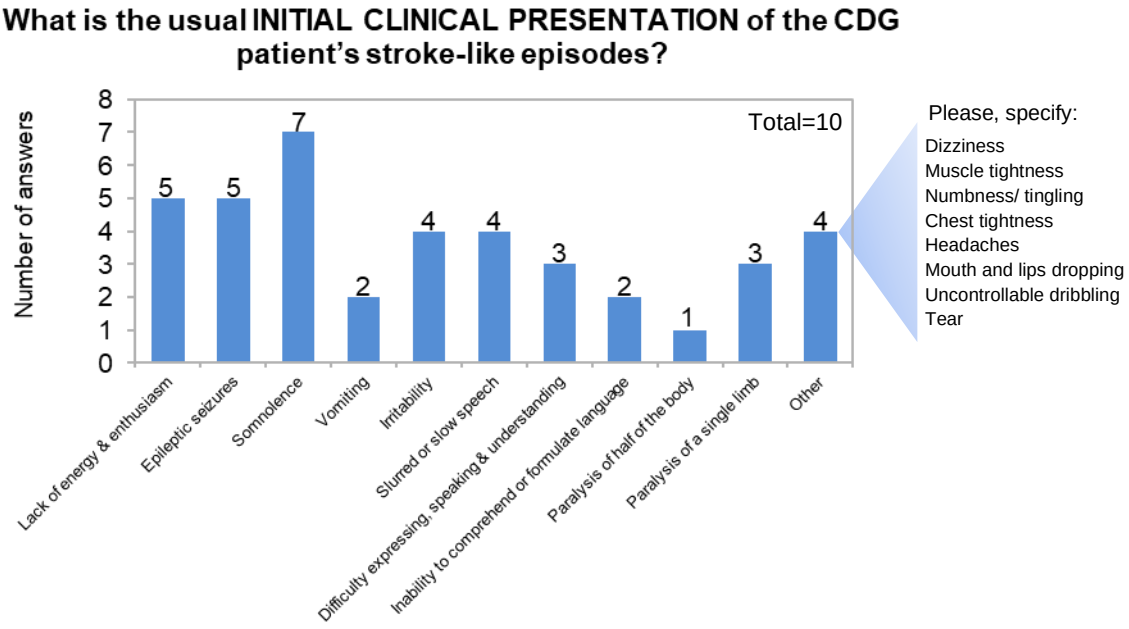

Figure 3.12. Initial clinical presentations of the CDG patient's stroke-like episodes. Somnolence was considered the most common initial clinical presentation (70%, n=7/10), followed by lack of energy & enthusiasm, epileptic seizures (50%, n=5/10 for both). A less significant number of respondents appointed irritability (40%, n=4/10), slurred or slow speech (40%, n=4/10), difficulty in expressing, speaking and understanding (30%, n=3/10) and paralysis of a single limb (30%, n=3/10) as initial SLE manifestations. Few participants reported the occurrence of vomiting, inability to comprehend or formulate language and paralysis of half of the body before the SLE (20%, n=2/10; 20%, n=2/10; 10%, n=1/10 respectively). Some participants chose the option 'Other' (40%, n=4/10) and specified the initial manifestations they noticed prior to the SLE: dizziness, muscle tightness, numbness/tingling, chest tightness, headaches, mouth and lips dropping, uncontrollable dribbling and/or tears.

3.3.3. Emotional/behavioral disturbances in CDG patients

CDG family members/caregivers frequently manifest their concern regarding emotional/behavioral disturbances.[37] Therefore, one of the survey sections focused on the patient's and caregiver's experience with this type of signs.

Respondents were presented with several examples of mood disturbances and were asked about their prevalence, severity and impact on the CDG patient's everyday life. (Figure 3.13)

As seen in Figure 3.13A, participants considered mood swings and repetitive behavior to be the most common in CDG patients (49%, n=29/59 for both). Tantrums and anxiety also seemed to be very common among the patients (44%, n=26/59 and 34%, n=20/59 respectively). A less significant number of participants appointed aggressive behaviour, autistic features and/or self-abusive behaviour (27%, n=16/59, 22%, n=13/59 and 14%, n=8/59 respectively).

Regarding symptom severity, most suggested manifestations were considered moderately severe by the participants.

When inquired about the impact of emotional/behavioral disturbances, the participants shared that all the signs presented had a minor to a moderate impact in the patient's everyday life, which can be seen in Figure 3.13B.

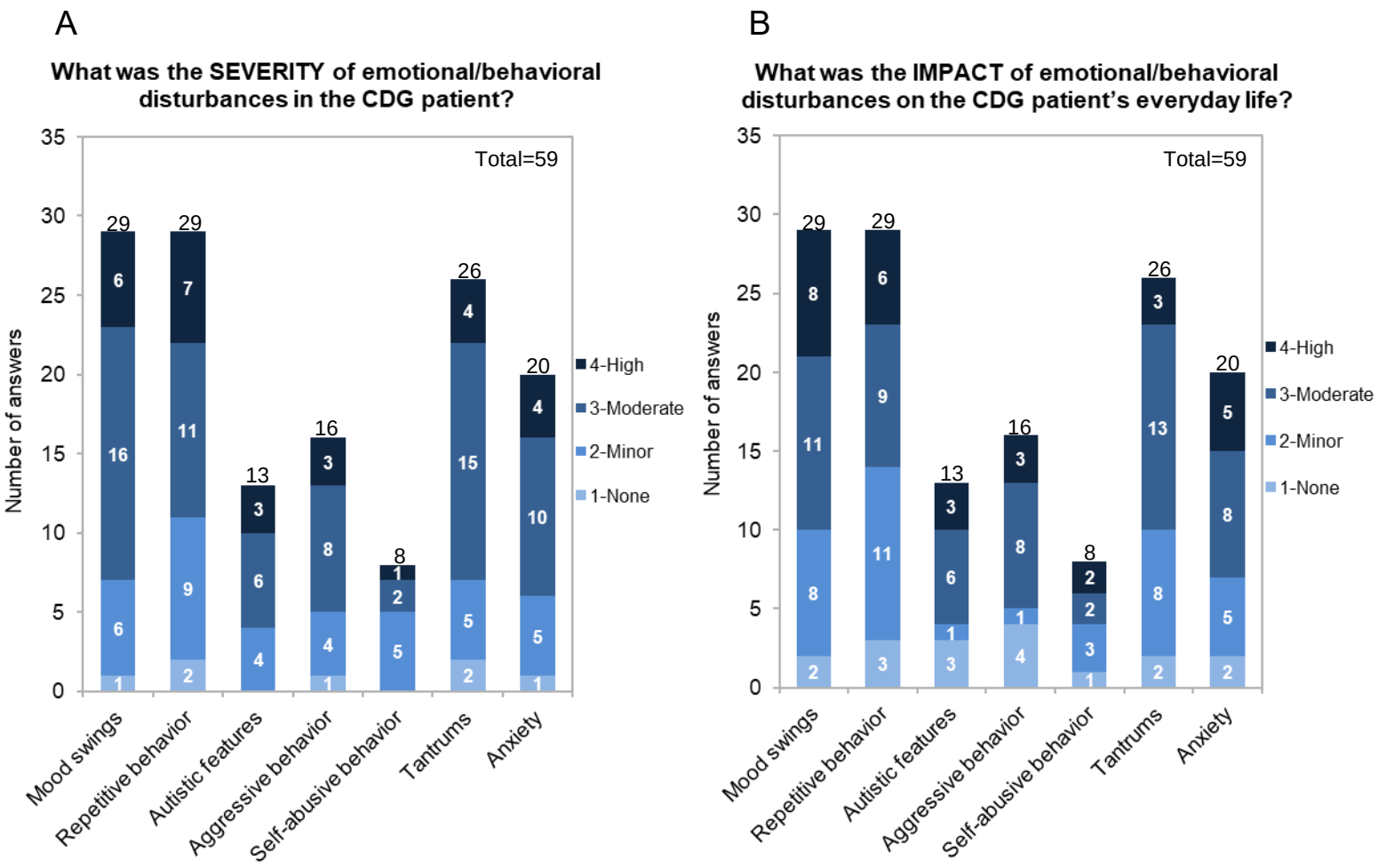

Figure 3.13 A) Severity and prevalence of emotional/behavioral disturbances in CDG patients, according to the survey respondents. Mood swings and repetitive behavior were considered the most common manifestations (49%, n=29/59 for both), followed by tantrums and anxiety (44%, n=26/59 and 34%, n=20/59 respectively). Aggressive behaviour, autistic features and/or self-abusive behaviour were the less common manifestations observed in the CDG patients (27%, n=16/59, 22%, n=13/59 and 14%, n=8/59 respectively). Regarding the severity of emotional/ behavioral disturbances, all participants considered them to be moderately severe. **B) Impact of emotional/behavioral disturbances in CDG patient's day-to-day.** Participants shared that all the suggested manifestations had a minor to a moderate impact in the patient's everyday life.

3.4. Ophthalmologic S&S

Ophthalmologic S&S are frequently observed in the CDG syndrome.[10] In fact, survey respondents considered the ocular system as the second most affected system in CDG. Therefore, a subchapter of this thesis was dedicated to this type of S&S.

The participants were presented with some examples of ophthalmological manifestations and were asked to describe their prevalence, severity and their impact in the patient's daily life. (Figure 3.14)
In terms of symptom prevalence, respondents considered strabismus to be the most common manifestation (72%, n=33/46) among the CDG patients. Involuntary, rapid and repetitive movement of the eyes (nystagmus) were disclosed by approximately half of the respondents (46%, n=21/46). The least common eye sign among the patients was retinitis pigmentosa (defective ability of the retina to

sense light), which was only reported by a quarter of the participants (24%, n=11/46).

When inquired about the severity of these eye manifestations, all participants considered them to be slightly or moderately severe, as seen in Figure 3.14A.

Regarding the impact of the ophthalmological manifestations presented, all seemed to have a minor impact or no impact at all in the patient's everyday life, which can be observed in Figure 3.14B.

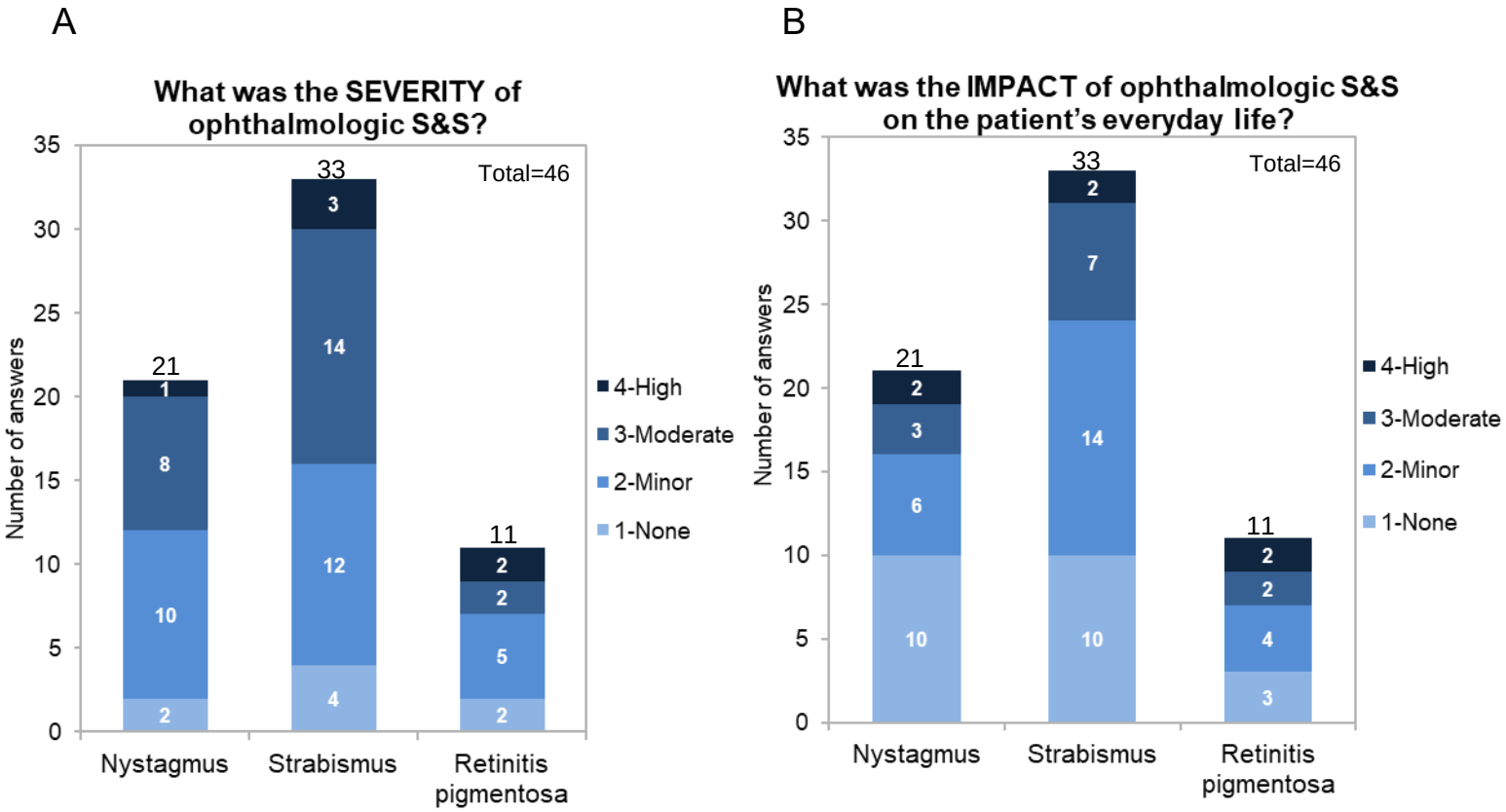

Figure 3. 14 A) **Severity and prevalence of ophthalmologic S&S in CDG patients.** According to the survey respondents, strabismus is the most common ophthalmological abnormality (72%, n=33/46), followed by nystagmus (46%, n=21/46). Retinitis pigmentosa was only reported by a quarter of the participants (24%, n=11/46). All participants considered these manifestations to be slightly to moderately severe. **B) Impact of ophthalmologic S&S in CDG patient's everyday life.** The majority of participants shared that all three manifestations had a minor impact in the patients day-to-day. A few even considered it to have no impact at all.

3.5. Gastrointestinal S&S

Since the survey respondents considered the gastrointestinal system as the third most affected system in CDG, it was decided to examine these signs more thoroughly. To accomplish this, participants were asked to share the frequency of the GIT manifestations the CDG patients presented (Figure 3.15) and to describe the severity and impact of GIT symptoms in the patient's day-to-day life (Figure 3.16).

Regarding the frequency of GIT signs, participants reported that gastroesophageal reflux (50%, n=10/20), diarrhea (45%, n=10/22), constipation (45%, n=10/22) and abdominal pain (43%, n=6/14) were the most recurrent manifestations in the CDG patients, whereas dysphagia was considered the

most persistent manifestation among the patients (67%, n=10/15). Respondents also shared that abdominal bloating (67%, n=8/12), nausea and vomiting (67%, n=6/9, 62%, n=13/21 respectively) only happened occasionally.

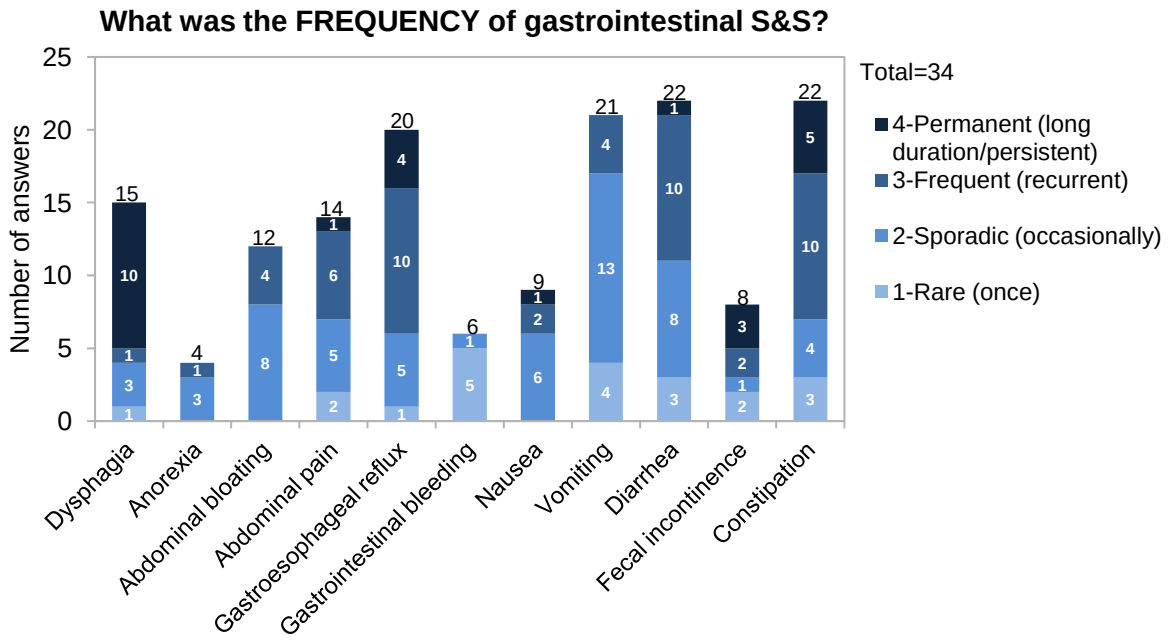

Figure 3.15. Frequency of gastrointestinal S&S in CDG patients. According to the survey respondents, gastroesophageal reflux (50%, n=10/20), diarrhea (45%, n=10/22), constipation (45%, n=10/22) and abdominal pain (43%, n=6/14) were the most common manifestations in CDG patients. Dysphagia seemed to be the most persistent manifestation (67%, n=10/15) while abdominal bloating (67%, n=8/12), nausea (67%, n=6/9) and vomiting (62%, n=13/21) only occurred occasionally.

When it comes to the severity of the GIT signs (Figure 3.16A), most participants considered dysphagia (60%, n=9/15) to be the most severe manifestation present in the CDG patients. Constipation (45%, n=10/22), abdominal pain (43%, n=6/14) and abdominal bloating (42%, n=5/12) were considered moderately severe by the majority of participants. The respondents also shared that vomiting (48%, n=10/21), diahrrea (45%, n=10/22) and gastroesophageal reflux (40%, n=8/20) were slightly severe. Regarding the impact of gastrointestinal S&S on the patient's everyday life (Figure 3.16B), most participants considered dysphagia (53%, n=8/15) to have a high impact on the patient's everyday life. Additionally, the majority of participants considered abdominal pain (43%, n=6/14), abdominal bloating (42%, n=5/12) and constipation (36%, n=8/22) to affect moderately the day-to-day of the patients. Signs like nausea (44%, n=4/9), diahrrea (41%, n=9/22) and vomiting (38%, n=8/21) were considered to have a minor impact in the patient's everyday life.

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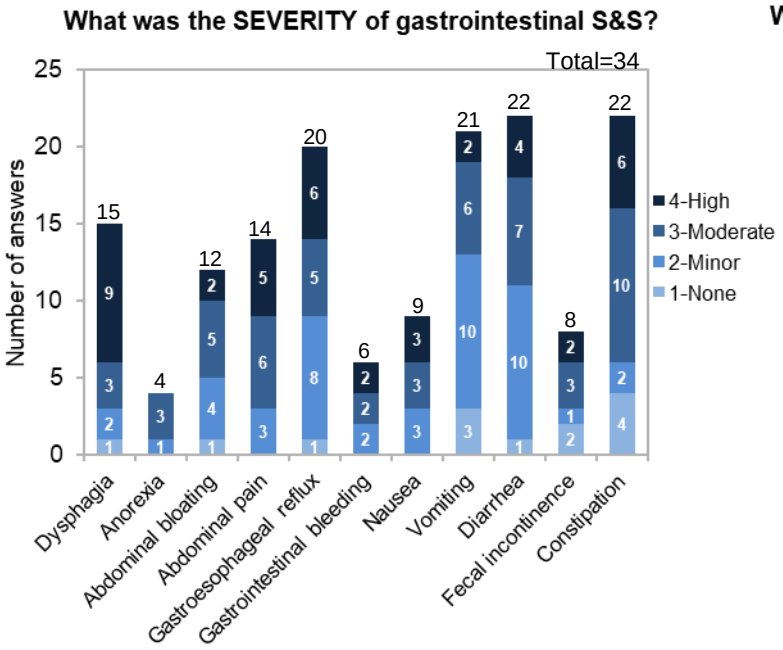

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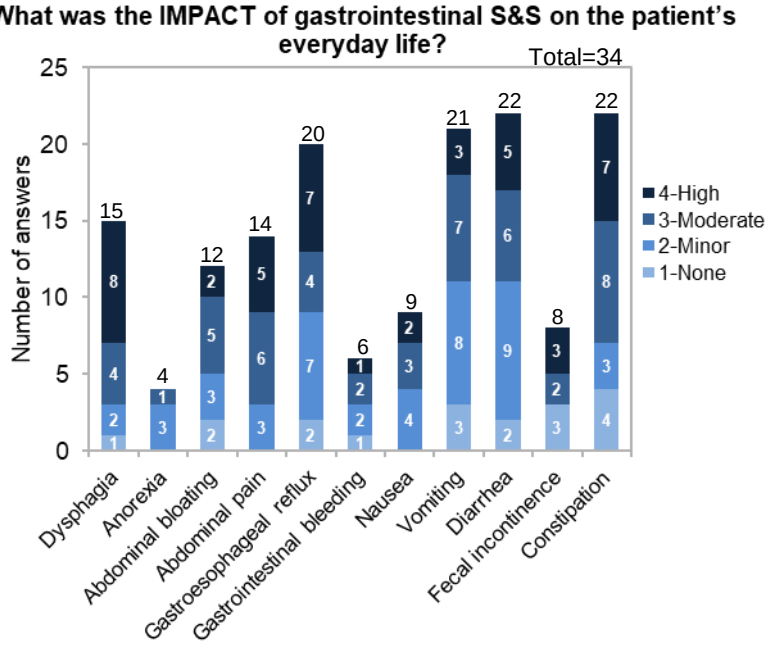

Figure 3.16 A) Severity of gastrointestinal S&S in CDG patients. According to the survey respondents, dysphagia seemed to be the most severe GIT manifestation (60%, n=9/15) whereas constipation (45%, n=10/22), abdominal pain (43%, n=6/14) and abdominal bloating (42%, n=5/12) were considered moderately severe. Participants also shared that vomiting (48%, n=10/21), diahrrea (45%, n=10/22) and gastroesophageal reflux (40%, n=8/20) were slightly severe. **B) Impact of gastrointestinal S&S in the everyday life of CDG patients.** Survey participants shared that dysphagia was very impactful in the everyday life of the patient (53%, n=8/15), while abdominal pain (43%, n=6/14), abdominal bloating (42%, n=5/12) and constipation (36%, n=8/22) had a moderate impact on the patient's everyday life. Additionally, nausea (44%, n=4/9), diahrrea (41%, n=9/22) and vomiting (38%, n=8/21) were considered to have a minor impact in the patient's everyday life.

3.6. Prioritizing CDG S&S to treat

At the end of the survey, the participants were presented with several manifestations from the different systems that can be affected in CDG and were asked to select the 5 most and least important S&S to prioritize in treatment development. (Figure 3.17)

Regarding the most important manifestations to prioritize in treatment development, the majority of participants considered intellectual delay (69%, n=45/65), gross motor disability (68%, n=44/65) and seizures (52%, n=34/65) as the most important S&S to treat. A less significant number of respondents also appointed fine motor disability (46%, n=30/65), speech problems (42%, n=27/65) and emotional/behaviour disturbances (34%, n=22/65) as important symptoms in need of treatment.

When it comes to the least important S&S prioritize in treatment development, participants selected infertility (55%, n=36/65), strabismus (49%, n=32/65), and abnormal menstrual cycles (42%, n=27/65) as the least important manifestations to prioritize in treatment development. Less significantly, nystagmus (37%, n=24/65) social problems (32%, n=21/65) and retinitis pigmentosa (28%, n=18/65) were also appointed as the least important S&S to be prioritized in therapeutical development.

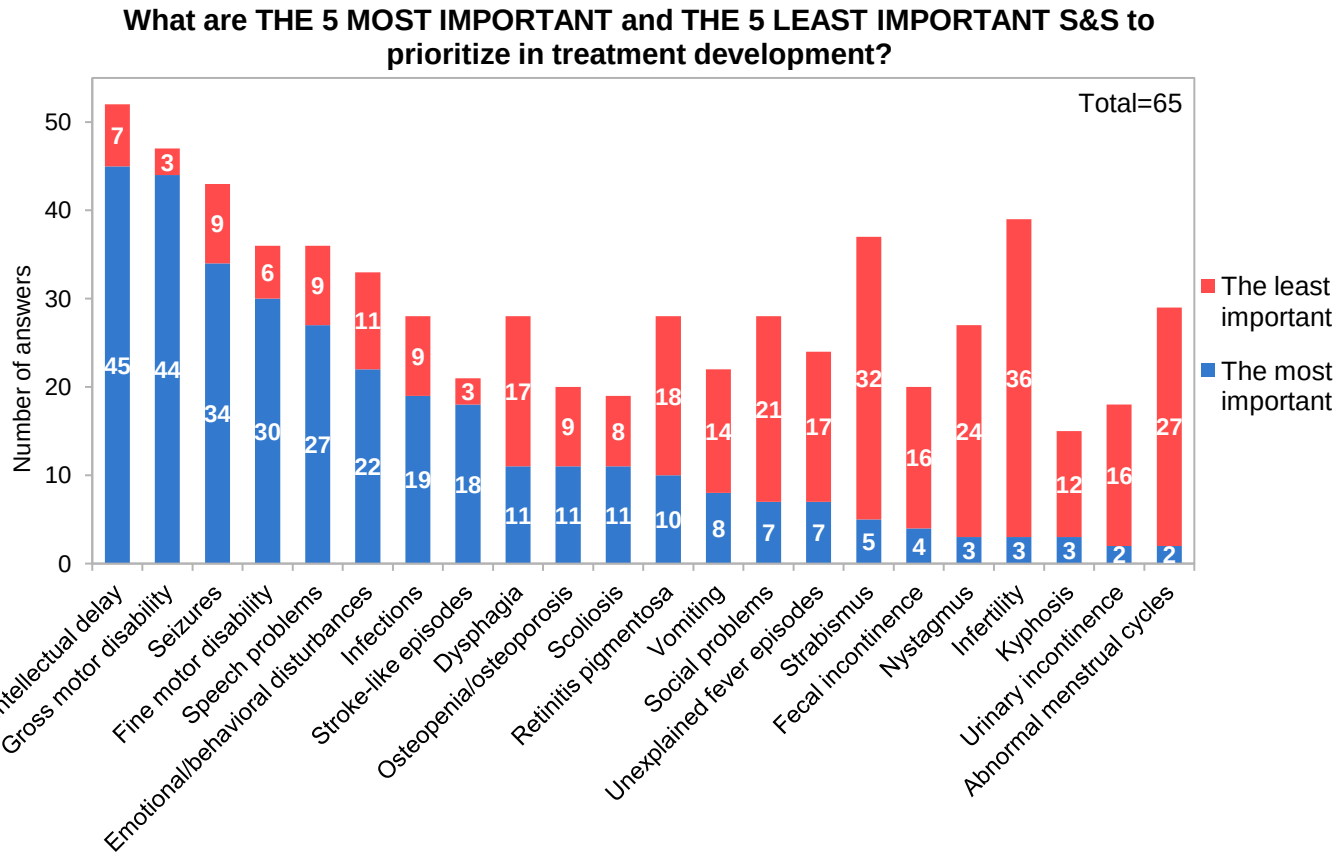

Figure 3.17. Signs and symptoms to prioritize in treatment development. According to the respondents, intellectual delay (69%, n=45/65), gross motor disability (68%, n=44/65) and seizures (52%, n=34/65) are the most important S&S in need of treatment. A less significant number of participants also selected fine motor disability (46%, n=30/65), speech problems (42%, n=27/65) and emotional/behaviour disturbances (34%, n=22/65) as the most important manifestations to prioritize in treatment developing. Furthermore, participants considered infertility (55%, n=36/65), strabismus (49%, n=32/65) and abnormal menstrual cycles (42%, n=27/65) as the least important S&S to treat. A less significant number of participants also appointed nystagmus (37%, n=24/65), social problems (32%, n=21/65) and retinitis pigmentosa (28%, n=18/65) as the least important manifestations to prioritize in treatment development.

Chapter 4. Discussion

Since glycosylated proteins and lipids perform crucial functions and are ubiquitously present in the body, CDG are characterized by a striking heterogeneity and complexity of S&S, which may affect multiple organs and systems.[12]

For that reason, the aim of this thesis was to explore CDG symptom variability and evaluate the severity and impact of CDG signs in patients and family members/caregivers, as well as, to identify the symptoms that require prioritized treatment and improved symptom management.

In this study, we utilised a people-centric approach to develop and apply a rigorous patient preference questionnaire, the CDGSPQ, targeting CDG patients and their family members/caregivers.

This patient-centred approach successfully allowed us to improve our knowledge on CDG phenotypic variability, to assess the impact of CDG symptoms in the patients and their family members' lives, as well as, to determine the priorities and unmet needs of the CDG community regarding treatment development and symptom management. Additionally, we were able to obtain relevant information regarding CDG patients and their caregivers' sociodemographic aspects.

The CDGSPQ questionnaire had a significant number of respondents, indicating the efficacy of the recruitment and dissemination campaigns implemented.

The survey participants were geographically dispersed, including people from more than twenty different nationalities. This is unsurprising, given that people living with rare diseases, such as CDG, are frequently dispersed across the globe.[38] It was also noticeable that some nationalities, like Brazilians and Americans, were more represented than others. This can be explained by the existence of well-established networks of patient organizations in these countries, which facilitated the dissemination of the survey among the CDG community and encouraged participation.[39]

The majority of the participants were parents, mainly mothers of people living with CDG. In fact, it is usually reported that the primary caregiver role for people living with rare diseases is usually assumed by the mother, as women tend to be more interested in health-related subjects and medicine and caregiving is still viewed as a feminine role.[40,41]

Two study participants shared that they were living with CDG. This shows that only a minimal part of our sample might not have very severe CDG manifestations, as they were able to represent themselves and share their perspective regarding their S&S.

Concerning the age range of the CDG patients, survey participants shared that most of them were of young age. This was not unexpected since most rare diseases have been known to begin during childhood.[42] Also, it may suggest that the patients are receiving earlier diagnoses nowadays, as the result of the progresses made in CDG research.

Taking into consideration the input given by the survey respondents, a thorough analysis of CDG S&S was conducted.

Results showed that neurological & muscular, ophthalmological and gastrointestinal S&S are the most common manifestations among the CDG patients.

Neurologic and muscular S&S dominate the clinical picture of most CDG types. Hence, it was already anticipated that the survey participants would regard this type of signs as the most significant clinical

manifestations in people living with CDG. Respondents reported that, among the neurological signs exhibited by the CDG patients, gross motor disability, intellectual delay, and speech problems were the most severe and impactful in the patients and their family members' daily life. This is not surprising, since these manifestations are very debilitating, impacting physical, social, and mental functioning as well as the ability to perform everyday activities.[19,31,43]

Even though they are mainly rare clinical events, acute CDG neurological manifestations, such as seizures and SLE, can also have a big impact in the quality of life of individuals with CDG and their families. [31]

Seizures stand out among CDG neurological S&S since they have been reported in almost all types of CDG. In fact, half of the survey participants reported seizures, which occurred mostly 1 to 3 times per year throughout the patient's life. However, an accurate description of seizures' semiology in CDG is yet to be established.[35] Since they can be unpredictable, it can be difficult to determine why seizures occur or what triggers them. Being familiar with seizures' potential triggers is especially important to help preventing them. Survey respondents contributed to a better understanding of this condition, as they selected the most common triggers they recognised in the CDG patients: episodes of illness/fever, tiredness/sleep deprivation and stress. These findings are consistent with previous research on seizures' clinical manifestations.[44]

Stroke-like episodes have been described as some of the most QoL-impacting issues in CDG patients and their family members/caregivers. SLE are considered to be quite challenging, since their risk factors and underlying pathomechanisms are yet to be identified and effective symptom management and treatment strategies are still unavailable.[31,36,45] Fortunately, out of the 65 survey participants, only 10 reported the occurrence of SLE. Unsurprisingly, those who experienced them, shared they had a high impact in the day-to-day life of the patient. Additionally, survey participants shared the most common triggers and initial clinical manifestations of SLE, thereby contributing to an improved comprehension of this symptom. SLE were typically triggered by infections, head trauma and/or illness/fever and their initial presentations most often included somnolence, seizures and lack of energy & enthusiasm. These results are in accord with previous studies concerning SLE's clinical features.[46]

Previous studies have recognized emotion dysregulation as a common manifestation in individuals with neurodevelopmental disorders.[47] The CDG community has also expressed concern regarding this dysregulation.[37] In fact, emotional and behavioral issues in CDG patients were perceived as moderately severe by survey respondents, with a fair impact on the daily lives of both the patients and their family members.

These results indicate the presence of emotional and behavioral disturbances that are somewhat impactful in CDG patients, highlighting the need for further research on this subject.

Many metabolic disorders present symptoms affecting the eye and the visual pathways.[48] CDG are no different and ophthalmological abnormalities, are frequently observed in the syndrome.[10] However, this ocular and visual involvement in CDG is still unexplored.[49] Strabismus was highlighted by survey participants, who appointed it as the most frequent ophthalmological manifestation. This fact is unsurprising since strabismus is considered a common dysmorphic feature in CDG patients.[19]

Even though eye manifestations' severity varied from minor to moderate, participants considered it to only have a minor impact in patients' daily life. These results suggest that ophthalmological S&S may not need to be prioritized at the moment.

In addition to neurological and eye manifestations, inherited metabolic diseases commonly include gastrointestinal manifestations.[50] This type of signs are commonly reported in CDG patients as well.[10] In fact, younger patients can exhibit this type of symptoms before some CDG typical features (p.e. neurological abnormalities and/or dysmorphology) are spotted.[51]

According to the survey participants, the most frequent GIT symptoms were gastroesophageal reflux, diarrhea, and/or constipation. Even though these symptoms were only rated as mildly to moderately severe, many survey participants considered their impact on CDG patients and their families' daily lives to be high. This might be explained by the discomfort these signs cause in CDG patients, as well as by the disruption they cause in both the patients and caregivers' daily lives.

Dysphagia was considered the most persistent GIT manifestation and its severity and impact in the patients' life was considered very high. This comes as no surprise since swallowing difficulties can have a detrimental effect on dietary intake and, thus, growth and development of the CDG patient. In most severe cases, the patient may need to get nutrition in other ways, using a tube inserted through their nose or into their stomach.[52]

This thorough symptom analysis not only confirmed the variability and heterogeneity of CDG's S&S, but also highlighted the importance of symptom prioritization in symptom management and treatment. Identifying the most pressing and significant CDG S&S is crucial to expedite and direct research towards managing or treating the symptoms that have the greatest impact on the patient's health and quality of life. Therefore, the survey respondents' direct feedback on which symptoms to prioritize holds significant value in this study.

Not surprisingly, the most important manifestations to prioritize were all neurologic & muscular S&S, such as intellectual delay, gross and fine motor disabilities, seizures, speech problems and emotional/behavior disturbances. This fact reinforces the negative impact that neurologic & muscular manifestations have in people living with CDG.

Regarding the least important signs in need of prioritization, participants selected reproductive problems, such as infertility and abnormal menstrual cycles, and strabismus, which was considered to have a small impact on the patient's day-to-day, as previously mentioned.

Considering that the impact of the CDG signs can vary significantly, there was good level of agreement within the perspectives of the study participants when it came to the identification of symptoms to prioritize. Additionally, the respondents' input contributed to a better understanding of CDG clinical manifestations, especially of neurologic signs.

However, given the small number of survey participants and CDG symptom heterogeneity, our results should be interpreted cautiously, as they are not representative of the full spectrum of CDG clinical manifestations.

In conclusion, the results of this preliminary study indicate that the use of people-centricity methodologies is a promising approach when it comes to S&S research and should be given greater importance in future CDG studies.

Chapter 5. Conclusions and Future Perspectives

In conclusion, this thesis underlines the importance of people-centred methodologies in advancing biomedical research, especially in the case of complex and heterogeneous diseases like CDG. Our patient-centred study not only confirmed previously literature findings regarding CDG S&S, but also, it created new insights on CDG symptom prioritization.

Results confirm the high prevalence of neurological and GIT S&S in the CDG syndrome and emphasize the adverse effects they can have in people living with CDG. In contrast, the significance of ophthalmological symptoms was downplayed, implying that they may not require immediate prioritization.

Additionally, our study results acknowledged neurological and muscular symptoms as the most important manifestations to prioritize in CDG research.

Lastly, our results reinforce the need of further S&S research in CDG to help guiding and accelerating therapeutic approaches and development.

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Chapter 6. References

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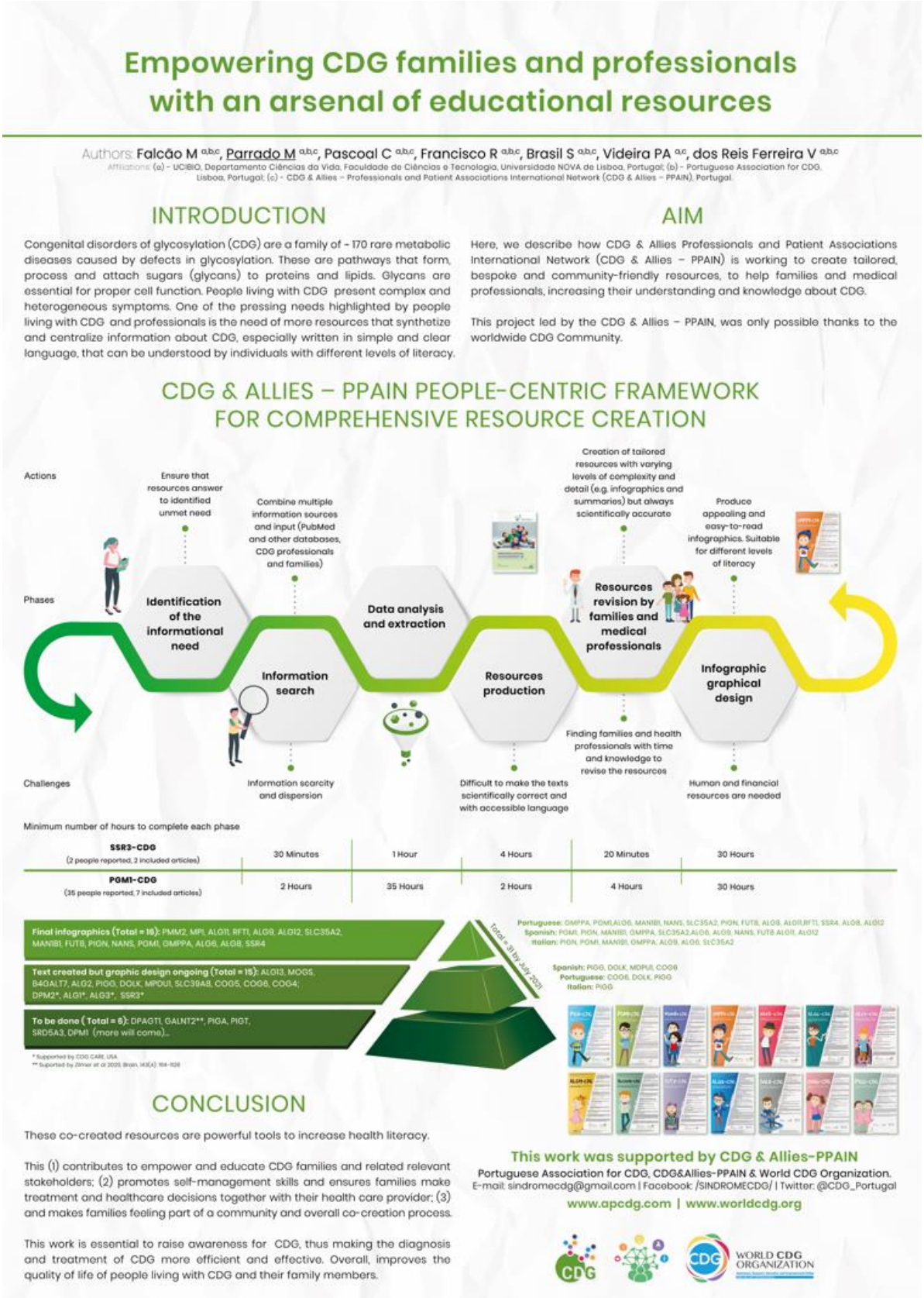
Chapter 7. Appendix

Appendix I: Poster “Empowering CDG families and professionals with an arsenal of educational resources”



Appendix II: Poster "A grassroots effort to build community practical tools using the International Clinical Guidelines for the Management of Phosphomannomutase 2-Congenital Disorders of Glycosylation (PMM2-CDG) – A case study transferable across all CDG types"

Appendix III: Ethical approval for the CDGSPQ from the ethical committee of the Faculty of Psychology of the University of Lisbon

Faculdade de Psicologia
UNIVERSIDADE DE LISBOA

DECLARAÇÃO

Para os devidos efeitos atesta-se que o projeto de investigação *"Prioritizing SymptomsImpacting Quality of Life for PMM2-CD Short name version: PMM2-CDG Symptom Prioritization Questionnaire – (PMM2-CDGSPQ)"*, apresentado pela Profª Doutora **Maria Luisa Torres Queiroz de Barros** foi apreciado favoravelmente na reunião de 24 de setembro de 2020 da Comissão de Deontologia da Faculdade de Psicologia da Universidade de Lisboa para a totalidade da sua duração (*janeiro 2021– outubro 2021*).

Lisboa, 12 de outubro de 2020

A Presidente da Comissão de Deontologia

UNIVERSIDADE DE LISBOA FACULDADE DE PSICOLOGIA

(Prof. Doutora Maria José Chambel)

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Appendix IV: Supplementary Tables

Supplementary Table 7.1 - Keyword combinations selected for the literature search about Diet & Management/ Rehabilitation Strategies applied to CDG and rare diseases with similar S&S and the number of results on PubMed.

Keywords	PubMed Results (26/05/2020)
("Food" OR "Food Habits" OR "Eating Habits" OR "Diet" OR "Dietary " OR "Nutrition" OR "Dietary Restrictions" OR "Food Supplements") AND ("Survey" OR "Questionnaire") AND ("Congenital disorder of glycosylation" OR "CDG" OR "Carbohydrate-deficient glycoprotein syndrome" OR "Deficient glycosylation" OR "Glycosylation deficiency" OR "Hypoglycosylation" OR "Rare diseases" OR "Rare metabolic diseases" OR "Inborn errors of metabolism" OR "Inherited metabolic diseases") AND ("Neurologic" OR "Cardiac" OR "Gastrointestinal" OR "Immunologic" OR "Hepatic" OR "Endocrine" OR "Hematologic" OR "Renal" OR "Ophthalmological" OR "Skeletal" OR "Behavioural problems" OR "Anxiety" OR "Hyperactivity" OR "Seizures" OR "Stroke-like episodes" OR "Pericardial effusion" OR "Cardiomyopathy" OR "Hepatomegaly" OR "Hepatosplenomegaly" OR "Liver steatosis" OR "Liver fibrosis" OR "Cirrhosis" OR "Anorexia" OR "Bulimia" OR "Gastroesophageal reflux" OR "Gastrointestinal bleeding" OR "Vomiting" OR "Diarrhea" OR "Ascites" OR "Abdominal bloating" OR "Failure to thrive" OR "Gastroparesis" OR "Protein-losing enteropathy" OR "Lymphangiectasia" OR "Intestinal inflammation" OR "Food intolerances" OR "Gluten intolerant" OR "Lactose intolerance" OR "Glucose intolerance" OR "FODMAP intolerance" OR "Food allergies" OR "Autoimmune diseases" OR "Celiac disease" OR "Inflammatory bowel disease" OR "Proteinuria" OR "Congenital nephrotic syndrome" OR "Osteopenia" OR "Hypoglycemia" OR "Hyperglycemia" OR "Sleep disturbances")	22
("Food" OR "Food Habits" OR "Eating Habits" OR "Diet" OR "Dietary " OR "Nutrition" OR "Dietary Restrictions" OR "Food Supplements") AND ("Congenital disorder of glycosylation" OR "CDG" OR "Carbohydrate-deficient glycoprotein syndrome" OR "Deficient glycosylation" OR "Glycosylation deficiency" OR "Hypoglycosylation") AND ("Neurologic" OR "Cardiac" OR "Gastrointestinal" OR "Immunologic" OR "Hepatic" OR "Endocrine" OR "Hematologic" OR "Renal" OR "Ophthalmological" OR "Skeletal" OR "Behavioural problems" OR "Anxiety" OR "Hyperactivity" OR "Seizures" OR "Stroke-like episodes" OR "Pericardial effusion" OR "Cardiomyopathy" OR "Hepatomegaly" OR "Hepatosplenomegaly" OR "Liver steatosis" OR "Liver fibrosis" OR "Cirrhosis" OR "Anorexia" OR "Bulimia" OR "Gastroesophageal reflux" OR "Gastrointestinal bleeding" OR "Vomiting" OR "Diarrhea" OR "Ascites" OR "Abdominal bloating" OR "Failure to thrive" OR "Gastroparesis" OR "Protein-losing enteropathy" OR "Lymphangiectasia" OR "Intestinal inflammation" OR "Food intolerances" OR "Gluten intolerant" OR "Lactose intolerance" OR "Glucose intolerance" OR "FODMAP intolerance" OR "Food allergies" OR "Autoimmune diseases" OR "Celiac disease" OR "Inflammatory bowel disease" OR "Proteinuria" OR "Congenital nephrotic syndrome" OR "Osteopenia" OR "Hypoglycemia" OR "Hyperglycemia" OR "Sleep disturbances")	65
("Food" OR "Food Habits" OR "Eating Habits" OR "Diet" OR "Dietary " OR "Nutrition" OR "Dietary Restrictions" OR "Food Supplements") AND ("PMM2-CDG" OR "PMM2 congenital disorder of glycosylation" OR "phosphomannomutase 2-congenital disorder of glycosylation" OR "CDG-Ia" OR "Jaeken disease" OR "Jaeken syndrome" OR "Phosphomannomutase 2 deficiency")	19
("Physical activity" OR "Physiotherapy" OR "Aquatic therapy" OR "Swimming" OR "Occupational therapy" OR "Speech therapy" OR "Music therapy" OR "Art therapy" OR "Equine therapy") AND ("Survey" OR "Questionnaire") AND ("Congenital disorder of glycosylation" OR "CDG" OR "Carbohydrate-deficient glycoprotein syndrome" OR "Deficient glycosylation" OR "Glycosylation deficiency" OR "Hypoglycosylation" OR "Rare diseases" OR "Rare metabolic diseases" OR "Inborn errors of metabolism" OR "Inherited metabolic diseases")	10
("Physical activity" OR "Physiotherapy" OR "Aquatic therapy" OR "Swimming" OR "Occupational therapy" OR "Speech therapy" OR "Music therapy" OR "Art therapy" OR "Equine therapy") AND ("Congenital disorder of glycosylation" OR "CDG" OR "Carbohydrate-deficient glycoprotein syndrome" OR "Deficient glycosylation" OR "Glycosylation deficiency" OR "Hypoglycosylation" OR "PMM2-CDG" OR "PMM2 congenital disorder of glycosylation" OR "phosphomannomutase 2-congenital disorder of glycosylation" OR "CDG-Ia" OR "Jaeken disease" OR "Jaeken syndrome" OR "Phosphomannomutase 2 deficiency")	7
Total	123

Supplementary Table 7.2 - Inclusion and exclusion criteria applied to filter the papers for the literature search about Diet & Management/ Rehabilitation Strategies in CDG and rare diseases with similar S&S.

Exclusion Criteria	Inclusion Criteria
• Articles not in English • Reviews • Articles and surveys/questionnaires not concerning CDG or other rare disease with similar symptoms • CDG dietary strategies and food supplementation articles with unknow CDG type	• Electronic surveys/questionnaires addressing diet and management/rehabilitation strategies in CDG or other rare disease with similar symptoms • Original research regarding diet and management/rehabilitation strategies in CDG or other rare disease with similar symptoms (including dietary studies made in animal models)

ADVANCING THE UNDERSTANDING OF CONGENITAL DISORDERS OF GLYCOSYLATION SYMPTOMS TO ACCELERATE THERAPIES

Madalena Parrado

2023