

Ketotic hypoglycemia in patients with Down syndrome: an example of extreme citizen science in biomedicine

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Ketotic hypoglycemia (KH) is an often-overlooked disorder with low blood sugar and accelerated fat burn, sometimes in association with a syndromic disease. The Facebook support group for members of the patient organization Ketotic Hypoglycemia International became the platform where a mom of a child with a hitherto unseen combination of Down syndrome and KH identified more families with stories similar to her own. This resulted in a citizens-initiated and citizens-driven project, where scientific experts from the organization's Scientific Advisory Board were invited in to participate. It was preliminarily estimated that 7% of children with Down syndrome have KH. The first scientific paper on the topic has been published, an animation video of the findings was produced, and the first pilot project is about to start, investigating in detail the prevalence of KH in a cohort of 70 children with Down syndrome in Denmark. This project is an example of parent-organization-driven research, where novel observations may arise, not firstly caught by the health care system. Acknowledgment of such observations by presentation and subsequent further research in co-production between parents in a patient organization and health care professionals is an example of co-produced health research or extreme citizen science in biomedicine.

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1. Introduction

Rare diseases are defined by the European Union as a disease affecting fewer than 1 in 2,000 people, where it is defined as a condition that affects fewer than 200,000 people in the US [1]. In Europe alone, it has been estimated that 30 million people live with one or more of the 7000 identified rare diseases, of which 70% of them start in childhood. Worldwide, rare diseases are estimated to affect more than 300 million people [2]. Rare diseases are often degenerative and life-threatening and frequently have long diagnostic odysseys, waiting for an average of 6-7 years from the onset of symptoms for an accurate diagnosis [3]. Despite advances in medicines, only 5% of rare diseases have approved treatment options. It has been estimated that 30% of the children born with a rare disease, will die before the age of 5 [4]. Due to the low prevalence of patients, research in the field of specific rare diseases is very limited, leading to the emergence of an urgent and need-driven approach to research.

Within the rare disease communities, the limited access to rare disease experts and the limited access to services and governmental support, may lead families to support or even initiate and lead clinical-initiated research themselves to fill in knowledge-gaps in the basic understanding of the disease. Through the power of social media, these rare disease community members are using their lived experiences to connect with each other and with researchers to set research priorities, raise funds, disseminate findings, and find treatments [5].

The involvement of the public in research has become central to health research policy in general in most developed countries [6], [7], [8]. International government guidance recommends having patients and the public represented as co-applicants in research applications and in research in general. This trend has created a shift from health research being done “to”, “about” and “for” the patients to research being carried out “with” or even “by” the patients [9], [10].

A higher level of citizen-ownership of the research process may be associated with the term co-creation, or co-production, in which researchers and members of the public work together through all steps of the research processes [11], [12], [13], [14]. Examples of rare disease patients and caregivers uniting to initiate and lead research to find a cure for themselves or their loved ones, work as examples of co-created or co-produced health research, between patients, relatives, and medical experts in general. These efforts have also been categorized as citizen science. The European Commission is defining citizen science as “scientific work undertaken by members of the general public, often in collaboration with or under the direction of professional scientists and scientific institutions” [15].

In the following presented project, we reject the notion that only credentialed and/or paid scientists can take part in, lead or shape how research questions are asked, data are collected results are interpreted, and findings are use [16]. Haklay divides “levels of citizen science” [13] into 4 stages: Level 1: Crowdsourcing; Level 2: Distributed Intelligence; Level 3: Participatory

Science; Level 4: Extreme Citizen Science. We will present an example of what was later identified as a case of co-created and co-produced research, which, using the terminology of citizen science, match level 4—Extreme citizen science, the most comprehensive level of participation. Level 4 is categorized as “collaborative science—problem definition, data collection and analysis” [13]. The citizen scientists, having defined the research question, collected the data and shaped the analysis, are therefore co-authors on the publication.

The following presented project was done with a high volunteer engagement from the citizen scientists, which is seen in their high participation level. The citizen scientists—in this case, parent carers—performed research tasks in all steps of the research process, similar to a research assistant/fellow: from formulating the research question, to data collection and analyses, to contributing to the writing of the scientific publication. Their high participation level has not been directly linked to high level of education, like often seen in extreme citizen science projects with a high participation level from citizen scientists. In projects characterized with a high citizen engagement, it is often citizens with high educational levels, like doctoral degrees from other fields of research, who participate [16]. In this project, the citizen scientists huge time investment allowed for research skills and competences to develop as the project went along. This research process is an example of high inclusiveness in citizen science, due to the combination of the volunteers having a low level of scientific knowledge in the project carried out with high levels of volunteer and participation engagement [16]. With our project, we are showcasing how scientific knowledge can be gained when citizen science puts research into the hands of parent caregivers, who have insights into concerns not previously addressed by academia, government agencies [16] and medical doctors.

2. Ketotic hypoglycemia in patients with Down syndrome

Ketotic hypoglycemia (KH) without an identifiable underlying metabolic or hormonal disease is historically named idiopathic KH (IKH). The prevalence is unknown, but IKH is considered the most frequent cause of hypoglycemia beyond the neonatal period. KH is largely preventable with a relatively easy management, but failure to recognize KH can lead to severely reduced outcome when frequent and severe. In 2020, the global reaching family organization Ketotic Hypoglycemia International (KHI) was established, with the mission to enhance the understanding of IKH for the benefit of children, parents, and families affected by IKH. KHI aims to support patients and their families by sharing knowledge about IKH, and to support the continued research into etiology, monitoring, and treatment [17]. Shortly after KHI's establishment, the organization got involved in several organization and family driven research projects, based upon the most urgent needs of the families. The first project united researchers and families from around the world in a co-produced review

paper, where KH for the first time got divided into two: physiological KH and pathological KH, recognizing the range of ketotic hypoglycemia often being more than normal variation [17]. The second project was aiming at investigating the potential association between KH and Down syndrome (DS). KH in DS has not been reported before in the literature, until the findings of this research project was published.

2.1 Methods

A web-based survey on KH in DS was published, which was created through a collaboration between family members and medical experts in KHI. The responses were evaluated for consistency with KH by two authors. Two DS patient histories with documented KH were shared in more details. The research process was analyzed and divided into 10 steps that shaped this scientific discovery, in a co-produced research process between affected families and medical experts.

2.2 Results

Survey data on 139 DS patients were obtained through various campaigns and collaborations with a DS organization on social media. After validation, 10 patients (7.2%) had reported episodes of documented hypoglycemia, ketosis, and/or symptoms compatible with KH beyond the neonatal period. Glucose concentrations ranged 1.2-2.9 mmol/L; beta hydroxybutyrate was up to 5.5 mmol/L during hypoglycemia. One girl had trisomy 21 with no response to i.m. glucagon also had a heterozygous Xp22.23 deletion including GYG2, which protein, glycogenin 2, is a substrate for glycogen synthase. Treatment with extended-release cornstarch was effective [18].

The research activities in KHI is an example of a need-driven approach to co-created research, where patients and their families, work in a close collaboration with medical experts in all steps of the research process. The process of this research-project can be broken down into 10 steps: (1) The beginning: The Danish mother Danielle Drachmann and her two children got diagnosed with idiopathic ketotic hypoglycemia—a diagnosis of exclusion. The search for answers led Drachmann to unite with two professors: One professor from industry and one professor leading the National Center for Complex Hypoglycemia at Odense University Hospital, Denmark. (2) The organization: The collaboration with the two professors led to the formation of KHI, the world's largest family organization for families affected by idiopathic ketotic hypoglycemia (IKH), with more than 1500 members united through the organizations' social media support group. One of the professors entered the organization to Chair the Board of Directors (BoD), while the other entered to Chair the Scientific Advisory Board (SAB). Leading medical experts in the field of complex hypoglycemia, from the specialties of endocrinology, pediatric endocrinology, and inborn error of metabolism united from all over the world in the SAB to advance the understanding of IKH alongside the families. Shortly after the establishment, the families started to identify gaps in current medical knowledge in relation to

diagnosis, clinical investigations, management, and monitoring. (3) The discovery: Melanie is a girl with DS, who got diagnosed with KH. Her mother, Austin Carrigg, entered the support group and contacted the organization with a suspicion about an association between DS and KH after seeing posts from families in the support group on social media. (4) The survey: No association between DS and KH was ever reported in the literature. SAB members supported the family organization to draft a survey. SAB members provided consultation on the survey draft. (5) The data: A survey was sent to DS organizations and families world-wide. (6) The findings: The results indicated an association between DS and KH. (7) The mice study: A SAB member found a mice-study supporting the findings, as the mice with a model of Down syndrome had deficient glycogen synthesis, causing decreased glucose stores in the liver. (8) The publication: A scientific paper written by Drachmann, Carrigg and medical experts of the SAB was published alongside an animated video abstract. (9) The dissemination: The findings and the research process attracted worldwide press attention, alongside 2617 downloads of the paper in the first 6 months (with an average annual download for Journal of Inherited Metabolic Diseases (JIMD) Reports: 441), ranking as the second most downloaded article in JIMD Reports in 2021. (10) The KHI experience: The first clinical trials are now under way involving a cohort of children with DS in Denmark. The research projects in the organization became the start of a research-ecosystem based on co-created citizen health science, where questions were raised and pursued scientifically (with varying levels of scientific preparation) by the families, strongly supported and guided by the leading medical experts affiliated with the organization.

3. Conclusion

We present a case of extreme citizen science in the family organization Ketotic Hypoglycemia International, from the establishment of the organization to the scientific publication. This is the first demonstration of a possible high prevalence of KH in DS. Even though the findings need to be confirmed in other research settings, identification of KH in DS could have a dramatic impact, as simple treatments with cornstarch, protein and frequent meals may prevent KH attacks and, analogous to other conditions with KH, improve growth, stamina and prevent overeating and obesity. GYG2 deletion may contribute to KH in DS, resembling glycogen storage disease type 0.

Our research is an example of co-produced and family-organization driven health research, later identified as extreme citizen science, where novel observations may arise, not firstly caught by the health care system. In this project, the families were leading research from the identification of the research question to the scientific publication. This approach can be adopted within any research and patient group. Acknowledgement of such novel observations by publication and subsequent further research is a good example of extreme citizen science in biomedicine.

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