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METABOLIC REPROGRAMMING: INNATE METABOLISM IS THE KEYSTONE FOR ETIOPATHOGENETIC INTERPRETATION OF MANY DISEASES

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Nothing is really difficult if you divide it into many small pieces

Henry Ford

Innate metabolism consists of a network of biochemical reactions that convert nutrients into small molecules called metabolites. Through this series of reactions and the resulting metabolites, cells generate macromolecules (proteins, lipids, nucleic acids), redox equivalents, and the energy they need to maintain cellular functions under normal circumstances. Under pathological conditions, cells undergo reprogramming of their metabolism to survive this change in their homeostasis.

The term “metabolic reprogramming” thus refers to a change in the metabolic processes of a cell or organism in response to induced homeostatic alterations. This process involves the modification of the use of energy resources, such as sugars, lipids, and proteins, by cells to adapt to new conditions that are classically pathological as well as physiological or environmental.

“Metabolic reprogramming” is a concept that has been developed and is particularly relevant and current in contexts, such as cancer, where cancer cells alter their metabolism to promote growth and survival, even under stressful conditions, such as hypoxia (low oxygen availability) or nutrient deficiency. It is well known that normal cells obtain their energy via first glycolysis in the cytosol, which is followed by mitochondrial oxidative phosphorylation under aerobic conditions. When oxygen is scarce, the cells rely on glycolysis rather than oxygen-consuming mitochondrial metabolism for energy supply. However, the metabolic pattern of tumors is different from that of normal cells. As first observed by Otto Warburg[1], the phenomenon that cancer cells prefer to carry out glycolysis in the cytosol, even in the presence of oxygen, is known as the “Warburg effect” or “aerobic glycolysis”.

Because the infinite proliferation of tumor cells requires a faster energy supply, the ATP production rate of glycolysis is much faster than that in oxidative phosphorylation. However, efficiency in ATP production per molecule of glucose is much lower via glycolysis. In fact, various central metabolic pathways can be dysregulated in cancer cells. This process can also involve the metabolism of fatty acids, proteins,

and other molecules (urea cycle) and can be mediated by genetic factors, epigenetics, and environmental signals. Metabolic reprogramming is thus a key mechanism for cellular plasticity and adaptation to changing conditions[2].

More importantly, emerging evidence indicates that cancer cells are able to suppress the anti-tumor immune response by competing for and depleting essential nutrients or otherwise reducing the metabolic fitness of tumor-infiltrating immune cells.

Both the innate and adaptive immune systems have now established roles in the host defense against cancers through various mechanisms, which are raising an unprecedented development of modern cancer immunotherapies. The innate immune system consists of different populations of immune cells, including macrophages, neutrophils, monocytes, eosinophils, basophils, and natural killer cells, which are responsible for innate immunity against pathogens to maintain homeostasis of the host. Indeed, immune cells are capable of sensing various signals in the microenvironment and turning on specific immune functions in response. More and more evidence has pointed out that the immune response is associated with dramatic modifications in tissue metabolism, including the depletion of nutrients, increased oxygen consumption, and the generation of reactive nitrogen and oxygen intermediates. Similarly, many metabolites in the tumor microenvironment, in turn, also influence immune cell differentiation and effector function. However, recent work has shown that immune cells compete with cancer cells and other proliferating cells in the microenvironment for nutrients. This suggests that metabolic interventions hold promise for improving the effectiveness of immunotherapies.

Previous studies showed that the modifications of cancer cell metabolism are, in part, due to the recruitment of many inflammatory and immune cells. Subsequently, more and more researchers have found that the aberrant metabolites or intermediates of cancer metabolism may play an important role in regulating the proliferation, differentiation, activation and function of immune cells. Recent studies have shown that our immune system is closely related to other metabolic functions (also in cancer cells) in a way that has never been realized before. Moreover, it is described as a new field called immune-metabolism. However, the actual process of how metabolic reprogramming and cancer immune response affect each other has not been completely understood[3].

However, after decades of cancer research, we can now say that metabolic reprogramming is also a hallmark of great interest in many other pathological conditions and beyond.

Allergic diseases are a group of chronic inflammatory disorders driven by abnormal immune responses. Extensive progress has been made in characterizing the crucial roles of metabolic reprogramming in the regulation of immune cell functions. Dendritic cells (DCs) play a key role in the initiation and progression of allergic diseases by modulating T-cell responses. As critical upstream regulators and effectors of allergic responses, the activation, migration, and function of DCs depend on metabolic reprogramming, and understanding the functional alterations of DCs during allergic responses and the mechanisms underlying their metabolic regulation is critical for the development of effective strategies for the prevention and treatment of allergic diseases[4].

Autoimmune diseases occur when the immune system abnormally attacks normal body tissues, causing inflammation and damage. Each autoimmune disease also has peculiar immune and metabolic dysfunction in terms of etiopathogenesis. In rheumatoid arthritis (RA), immune cells exhibit different metabolic patterns and peculiar and specific mitochondrial/lysosomal dysfunction at different stages of the disease. In systemic lupus erythematosus, metabolic dysregulation of immune cells caused by type I interferon (IFN) causes activation of metabolic alterations that can worsen the disease. In primary Sjögren's syndrome, immune cell metabolism is altered, and mitochondrial damage can lead to cell and tissue damage. In systemic sclerosis, mitochondrial alterations affect fibroblast metabolism and immune response. Finally, alterations attributable to metabolic and mitochondrial problems are also known to occur in patients with idiopathic inflammatory myopathies. Metabolic reprogramming links cellular energy requirements and immune dysfunction, causing inflammation, damage, and symptoms in these diseases. It also affects immune cell functions such as differentiation, proliferation, and secretion. Therefore, the enormous potential of targeting metabolic pathways is evident[5].

Mitochondrial metabolic reprogramming also appears crucial in diabetic kidney disease (DKD). DKD, known as a glomerular disease, arises from a metabolic disorder that impairs renal cell function. Recent studies indicate that mitochondrial metabolic reprogramming has a significant impact on the pathophysiological progression of DKD. Alterations in renal metabolism led to abnormal expression of signaling molecules and activation of pathways, inducing oxidative stress-related cell damage, inflammatory

responses, apoptosis, and autophagy irregularities, culminating in renal fibrosis and functional insufficiency. Therapeutic interventions targeting renal metabolic reprogramming can potentially delay DKD progression[6].

Metabolic reprogramming in arginine methylation is relevant in various diseases, including cancer, cardiovascular diseases, chronic obstructive pulmonary disease, neurodegenerative disorders, viral infections and respiratory disease. Arginine methylation, a vital post-translational modification, plays a pivotal role in numerous cellular functions such as signal transduction, DNA damage response and repair, regulation of gene transcription, mRNA splicing, and protein interactions. Central to this modification is the role of protein arginine methyltransferases, which have been increasingly recognized for their involvement in the pathogenesis of various respiratory diseases and revealed an enormous potential as therapeutic targets[7].

Metabolic reprogramming is a process that involves the upregulation of different metabolic pathways in cells to balance energy, alter their phenotype and produce differentiation requirements. In this light, the role of metabolic reprogramming is particularly suggestive in the case of astrocyte function. Astrocytes are crucial for the maintenance of neuronal activity, and their activation occurs within minutes of the onset of ischemic stroke and subsequent inflammatory damage, that is, cerebral ischemia-reperfusion (I/R) injury. Activated astrocytes, also known as reactive astrocytes, are divided into two different phenotypes: astrocytes A1 (pro-inflammatory) and A2 (anti-inflammatory). A1 astrocytes have neurotoxic effects, whereas A2 astrocytes support the survival of neurons and promote tissue healing. A1 and A2 astrocytes show different metabolic reprogramming, such as glycolysis, glycogenolysis and glutamate uptake. Numerous scientific evidence suggests that manipulation of energy metabolism homeostasis can induce astrocytes to switch from the A1 to the A2 phenotype, highlighting how metabolic reprogramming in reactive astrocytes in the pathophysiological context of cerebral I/R may be a potential therapeutic target for cerebral I/R injury[8].

Finally, metabolic reprogramming is also relevant in skeletal and dental cell differentiation. Skeletal remodeling is a process that requires enormous amounts of energy and is associated with altered metabolic activities. Metabolic pathways of bone and dental tissue cells show fluctuating activities during bone loss and defects, suggesting regulated metabolic plasticity. These metabolic changes are often associated with epigenetic modifications, including changes in the expression or activity of enzymes modified by epigenetic mechanisms, which have a direct or indirect impact on cellular metabolism. Metabolic reprogramming induced by bone and dental conditions alters the epigenetic landscape by modulating the activities of DNA- and histone-modifying enzymes at the metabolite level. Epigenetic mechanisms, in particular acetylation and methylation, modulate the expression of metabolic genes, thereby influencing the metabolome. The interplay between epigenetics and metabolomics is crucial for the maintenance of bone and dental homeostasis, preserving cell proliferation and pluripotency. Metabolic therapies based on enzymes that modify chromatin metabolism, as well as dietary compounds that are active as epigenetic modulators, are envisaged as clinical treatments for bone and dental diseases[9].

Metabolic pathways are extremely complex and very often redundant. It is, therefore, appropriate to ask why nature has chosen such complex solutions for sometimes solving simple biochemical transformations. One possible answer stems from the considerations outlined above in relation to metabolic reprogramming. Indeed, it seems that evolution has ensured boundless possibilities for recovery and reorganization of functions under conditions of physiological stress or actual pathological alteration that can ultimately be traced back to complex metabolic disease.

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No artificial intelligence-assisted technologies were used in the production of this article.

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The author declares that he has no conflict of interest to disclose.

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ADOLESCENT PERCEPTIONS OF HEALTHCARE SERVICES FOR INHERITED METABOLIC DISORDERS AND GENETIC DISEASES: INSIGHTS FROM A SURVEY IN A PEDIATRIC HOSPITAL

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***ABSTRACT* – Objective:** To evaluate adolescent perceptions of healthcare services for Inherited Metabolic Disorders (IMDs) and genetic diseases in a tertiary pediatric hospital, identifying key elements for tailoring care to this unique patient group.

Patients and Methods: A survey comprising 29 questions, adapted from a validated tool, was distributed to adolescent patients (aged 12–18 years) with IMDs or genetic disorders at the Pediatric Hospital "Giovanni XXIII" of Bari (Italy). Data collection occurred between January and June 2022. Key domains included communication and information, facility quality, waiting times, visit durations, and illness experience. Descriptive statistics were employed, and statistical significance was set at $p<0.05$.

Results: Among 40 eligible participants, 27 completed the survey (response rate: 67.5%). Satisfaction was highest in communication and information (69.2%) and illness experience (69.8%), whereas waiting times received the lowest ratings (55.3%). Facility quality was rated positively overall (64.7%), with suggestions for improvements in personal spaces and age-appropriate facilities. More than half of respondents advocated for the inclusion of psychologists and patient association representatives in the care team. Notably, 62.3% supported teleconsultations, and 70.4% endorsed social media for improving disease management. Satisfaction levels did not significantly vary by age or hospital proximity.

Conclusions: Adolescents generally perceive hospital services positively but highlight areas for improvement, including reduced waiting times, expanded multidisciplinary care, and the introduction of telemedicine. Addressing these needs could enhance engagement and ensure adolescent-friendly healthcare services in IMD management.

Keywords: Metabolic disorders, Adolescence, Hospital management, Healthcare services.

List of Abbreviations: HEEADSSS: Home, Education and Employment, Eating, peer-related Activities, Drugs, Sexuality, Suicide/depression, and Safety from injury; IMD: Inherited Metabolic Disorder; MetabERN: European Reference Network for Hereditary Metabolic Disorders; SD: Standard Deviation.

INTRODUCTION

Inherited Metabolic Disorders (IMDs) result from enzymatic deficiencies caused by genetic defects in biochemical pathways. Consequently, toxic substrates or metabolites may accumulate, while essential products may become deficient, leading to complications in organs, such as the liver, brain, heart, muscle, and kidneys. These complications may manifest at various stages of life, either early or later in development[1].

Comprehensive diagnosis and treatment include regular and careful monitoring and follow-up throughout the patient's lifetime, necessitating several accesses in the hospital, both in inpatient and outpatient settings.

Advances in newborn screening and therapies have enabled earlier diagnosis and treatment, allowing many patients to survive into adulthood[2].

Adolescence is a particularly complex period marked by cognitive, physical, emotional, and social maturation[3].

In the case of clinical conditions, such as IMDs and genetic diseases, "healthcare assistance" faces an additional challenge for adolescents as they shift from parental care to independent self-management. This period is often accompanied by feelings of anxiety and inadequacy, which may lead to decreased compliance and disengagement from treatment. The healthcare assistance, in this period of life, needs to take into consideration psychosocial development, including the ability to consolidate identity, achieve independence, and establish adult relationships. To address these challenges, individualized support should be provided by specialized centers through multidisciplinary teams comprising clinicians, dietitians, and psychologists[4].

Guidelines emphasize the importance of patient-centered care that addresses adolescents' unique psychosocial needs. The HEEADSSS psychosocial interview framework—covering the domains of Home environment, Education and employment, Eating, peer-related Activities, Drugs, Sexuality, Suicide/depression, and Safety from injury – serves as a valuable tool for assessing adolescents' mental, emotional, and social health[5].

Despite these recommendations, adequate services, including standardized operating procedures and specific training for adult physicians specializing in IMDs, remain underdeveloped in Europe. A survey conducted by Stepien et al[6] among all 77 centers of the European Reference Network for Hereditary Metabolic Disorders (MetabERN) revealed that most respondents were metabolic pediatricians, and only approximately 40% had received formal training in managing adolescent metabolic patients. Moreover, compared to primary care settings, the quality of specialized assistance provided to hospitalized adolescent patients has been poorly documented. This study aims to evaluate perceptions of healthcare services of adolescent patients affected by IMDs and genetic diseases, referring to a tertiary care pediatric hospital. The goal is to identify key elements useful for delivering appropriately tailored care to adolescent patients.

PATIENTS AND METHODS

An online survey with 29 questions (see **Supplementary Material**) was distributed to patients from the Department of Metabolic and Genetic Disorders of the Pediatric Hospital "Giovanni XXIII" in Bari (Italy) between January and June 2022. Patients aged between 12 and 18 years were included.

The survey was based on a previously validated questionnaire[7], which comprises five sections, including general information and four areas investigated: communication and information, facility quality, waiting times and the duration of visits and their illness experience.

Patients were contacted by phone up to two times. Those who accepted to participate in the survey signed informed consent and were asked to complete a survey on the Google Forms platform by receiving a QR code via email. Patients independently completed the questionnaire.

Ethical approval was obtained from the Independent Ethics Committee of the Policlinico University Hospital of Bari, Italy (Prot. No. 0063763).

Statistical analysis

The responses were converted into scores (see **Supplementary Material**) and analyzed using descriptive statistics, with data presented as rating percentages (total score obtained/total score max) and averages (mean ± standard deviation). The chi-square test was used for nominal variables, and the Student's *t*-test was applied for continuous variables. A $p<0.05$ was considered statistically significant. Data analysis was carried out using the software Stata MP17 (StataCorp LLC, College Station, Texas, USA).

RESULTS

General information

Out of 40 patients recruited, 27 completed the survey (response rate 67.5%). Thirteen out of 27 (48.1%) patients were aged 12–13 years, 4/27 (15%) were 14–15 years old and 10/27 (37%) were 16-17 years. Ten were female (37%), 17 were male (63%). Of the 27 patients, 3 (11.1%) had a genetic disorder, while the remaining 24 (88.9%) were affected by an IMD. Among patients with IMDs, 18 (75%) were affected by PKU, one had urea cycle disorder (OTC deficiency), one was affected by hereditary fructose intolerance, two by cystinuria and two by hereditary lipid disorders (sitosterolemia and cholesteryl storage disorder).

Six out of 27 patients (22%) reported living <15 km as a distance between their residence and the hospital, 6/27 (22%) reported a distance between 15 km and 30 km, while 15/27 (55%) of respondents live >30 km distant from the hospital.

In the Information and Communication category, patients provided favorable feedback, with a rating of 69.2%, achieving a total score of 467 out of a maximum of 675 points. This corresponds to a mean score of 17.30 ± 2.76 on a scale ranging from 0 to 25. The Experience of the Illness category showed a rating of 69.8%, a total score of 226 out of 324, and a mean score of 8.37 ± 1.76 within a range of 0 to 12. The Quality of the Structure received a moderately positive evaluation, with a rating of 64.7%, a total score of 297 out of 459, and a mean score of 11.00 ± 1.84 on a scale from 0 to 17.

The waiting times category received a lower rating of 55.3%, with a total score of 269 out of 486 and a mean score of 9.96 ± 2.16 within a range of 0 to 18. For the facility quality category, a rating of 64.7%, with a total score of 269/486 and a mean score of 11.00 ± 1.84 within a range of 0–17, was reported. The category concerning the illness experience received a rating of 69.8% based on a total score of 226/324 and was associated with a mean score of 8.37 ± 1.76 on a scale of 0 to 12.

The overall satisfaction rating was 64.7%, with an aggregate score of 1259 out of 1944 points, translating to a mean total score of 46.63 ± 6.01 on a scale of 0 to 72. The scores assigned to individual questions, response categories, and the overall score were consistent across age groups and the distance from their residence to the hospital (p>0.05) (see **Supplementary Material**). Rating distribution according to areas investigated is summarized in Table 1. A more detailed description of responses for each question in each category is summarized in Table 2.

Information and Communication

Patients expressed a high level of satisfaction with aspects related to communication and the provision of information. The information received about their health status was well-rated, with a mean score of 2.44 ± 0.51, corresponding to 81.5% of the maximum score. Similarly, the collaboration among staff received positive feedback, scoring 2.26 ± 0.59 (75.3%). Patients felt welcomed by the healthcare staff, reflected in a score of 3.04 ± 0.85 (75.9%) and rated positively the answers provided when asking questions about their health or proposed treatment (2.33 ± 0.62, 77.8%). Respect for privacy was also favorably evaluated, with a score of 2.41 ± 0.50 (80.2%). Patients gave lower scores about being left alone with the doctor during visits (score 1.15 ± 0.86, 38.3%) and about their involvement in scheduling medical visits, rated at 1.81 ± 0.83 (60.5%). The impact of hospital visits on free-time activities, such as homework, hobbies, or socializing, also scored moderately at 1.85 ± 0.91 (61.7%).

Table 1. Rating distribution according to areas investigated.

	Percentage of the maximum score	Total Vote/Max	Expected score range	Mean ± SD
Information and Communication	69.2%	467/675	0-25	17.30 ± 2.76
Waiting times	55.3%	269/486	0-18	9.96 ± 2.16
Facility quality	64.7%	297/459	0-17	11.00 ± 1.84
Illness experience	69.8%	226/324	0-12	8.37 ± 1.76
Overall satisfaction	**64.7%**	**1259/1944**	**0-72**	**46.63 ± 6.01**

Table 2. Survey results for each question of areas investigated.

Area	Question	Expected score	Rating (%)	Mean ± SD
Information and Communication	How do you rate the information you received about your health status?	From 0 to 3	81.5%	2.44 ± 0.51
	How did you find the collaboration among the ward staff?	From 0 to 3	75.3%	2.26 ± 0.59
	How welcomed do you feel by the healthcare staff when you come to this hospital?	From 0 to 4	75.9%	3.04 ± 0.85
	How do you rate the answers provided to you when asking questions about your health or the proposed treatments?	From 0 to 3	77.8%	2.33 ± 0.62
	How do you evaluate the respect for your privacy when personal information is provided?	From 0 to 3	80.2%	2.41 ± 0.50
	How much would you like to be left alone with the doctor during the visit?	From 0 to 3	38.3%	1.15 ± 0.86
	How involved do you feel in deciding the timing of medical visits at the hospital?	From 0 to 3	60.5%	1.81 ± 0.83
	To what extent do medical visits interfere with your free time activities (homework, going out with friends, hobbies, sports, etc.)?	From 0 to 3	61.7%	1.85 ± 0.91
Waiting times	How do you evaluate the frequency of your hospital visits?	From 0 to 3	71.6%	2.15 ± 0.46
	How did you find the waiting time between entering the hospital and the medical visit?	From 0 to 4	41.7%	1.67 ± 0.68
	How did you find the duration of medical visits at the hospital?	From 0 to 4	48.1%	1.93 ± 0.38
	How did you find the waiting time between the end of the visit and discharge?	From 0 to 4	52.8%	2.11 ± 0.75
	How did you find the duration of hospitalization/ therapy (day service/day hospital)?	From 0 to 3	70.4%	2.11 ± 0.58
Facility quality	How suitable does the hospital environment seem for your age?	From 0 to 4	57.4%	2.30 ± 0.61
	How do you rate the organization of spaces dedicated to managing metabolic diseases?	From 0 to 3	67.9%	2.04 ± 0.59
	How do you evaluate the presence of children around you in this hospital?	From 0 to 3	79.0%	2.37 ± 0.49
	How did you find the spaces dedicated to you (e.g., phone charging stations, free seating, privacy for phone calls, etc.)?	From 0 to 4	61.1%	2.44 ± 0.85
	How do you feel about the possibility of being treated at an adult hospital?	From 0 to 3	61.7%	1.85 ± 0.66
Illness experience	How involved did you feel in decisions regarding your therapy and follow-up appointments?	From 0 to 3	76.5%	2.30 ± 0.54
	Do you feel capable of managing your illness and its therapy independently?	From 0 to 3	63.0%	1.89 ± 0.70
	How important do you consider the treatment of your condition?	From 0 to 3	92.6%	2.78 ± 0.42
	How limiting do you find your condition in your daily life?	From 0 to 3	46.9%	1.41 ± 1.01

Waiting times

While the frequency of hospital visits was rated positively at 2.15 ± 0.46 (71.6%), the waiting time before medical visits scored 1.67 ± 0.68 (41.7%), and the duration of medical visits, rated at 1.93 ± 0.38 (48.1%). The waiting time between the end of the visit and discharge received a moderate score of 2.11 ± 0.75 (52.8%), while the duration of hospitalization/therapy was rated at 2.11 ± 0.58 (70.4%).

Facility quality

Patients considered the environment suitable for their age, scoring 2.30 ± 0.61 (57.4%), and rated the organization of spaces dedicated to metabolic disease management at 2.04 ± 0.59 (67.9%). The presence of children in the hospital was also positively rated (2.37 ± 0.49, 79%). Personal spaces, such as areas for phone charging and privacy, were evaluated at 2.44 ± 0.85 (61.1%). The idea of being treated in an adult hospital scored comparatively lower at 1.85 ± 0.66 (61.7%).

Illness experience

Patients expressed a strong sense of the importance of their care and treatment, with the perceived importance of treating their condition scoring 2.78 ± 0.42 (92.6%). Involvement in decisions regarding therapy and follow-up appointments was also rated positively, with a score of 2.30 ± 0.54 (76.5%). Autonomy in managing their condition independently was rated moderately at 1.89 ± 0.70 (63.0%), and the perceived limitations of their illness on daily life scored relatively low at 1.41 ± 1.01 (46.9%).

Furthermore, concerning the question "Which professional figure would you add to the current follow-up team?", for 44.4% of patients (12 individuals), the current follow-up team, consisting of a physician, nurse, and dietitian, meets their needs. A total of 55.6% of adolescents (15 individuals) view the addition of "another professional figure" to the team positively. Specifically, 37% of patients (10 individuals) would find it useful to expand the team to include a representative from the Rare Metabolic Diseases Association, while 44.4% of patients (12 individuals) would like the inclusion of a psychologist. Seven patients (25.9%) consider the support of both professionals beneficial for the follow-up team. The results are summarized in Table 3. Responses did not differ by age ($p>0.05$), whereas greater satisfaction with the composition of the follow-up team was reported by patients living farther from the hospital ($p>0.05$) (see **Supplementary Material**).

Finally, the possibility of introducing remote teleconsultations in addition to in-person visits was supported by 62.3% of participants (17/27). Furthermore, 70.4% (19/27) believed that better use of social media could improve disease management both within and outside the hospital. The responses to these questions did not vary by age or distance from the hospital ($p>0.05$) (see **Supplementary Material**).

DISCUSSION

By evaluating perceptions of healthcare services in terms of communication and information, facility quality, waiting times, duration of visits and illness experience, this survey has identified key elements for delivering appropriately tailored care to adolescent patients with IMDs.

Table 3. Distribution of responses to the question: "Which professional figure would you add to the current follow-up team?"

Response	n	Percentage (%)
None	12	44.4%
Would add only a Representative from the Rare Metabolic Diseases Association	3	11.1%
Would add only a psychologist	5	18.5%
Would add both	7	25.9%

This study revealed that while adolescent patients generally appear satisfied with the care received in a pediatric hospital, there is considerable room for improvement to better meet their needs. Patient satisfaction levels align with findings from other studies[7,8]. However, it has been demonstrated that patient satisfaction and their perception of care do not always correspond to high-quality care delivery[9].

Adolescents expressed a particular appreciation for communication and information. This finding highlights that the attention given to these aspects is positively regarded and valued by this patient group. Such attention likely enhances compliance with the provided care, making it easier for adolescents and their parents to return for follow-up visits[10].

However, evaluations of waiting times and visit durations were less favorable. Specifically, less than half of the patients (41.7%) considered the waiting time between entering the hospital and the start of the medical visit to be acceptable, while only 48% deemed the duration of the visit appropriate. These findings highlight an opportunity to improve patients' and parents' perceptions of care quality. It is well-established that shorter waiting times enhance adherence to medical visits, especially among adolescents, who are generally less inclined to wait. Reducing waiting times could encourage greater engagement in medical care[11].

Another important area of focus is the composition of the follow-up team, currently consisting of a physician, nurse, and dietitian. More than half of the adolescent patients expressed dissatisfaction, preferring the inclusion of additional professional figures, such as a representative from a patient association, a psychologist, or both. Adolescence is a particularly sensitive period for psycho-physical development, which becomes even more complex for individuals with chronic illnesses. Generally, adolescents are reluctant to seek psychological support. Therefore, the expressed need for psychological support by patients in this hospital – contrary to the general trend – is a critical point that warrants further exploration to deliver high-quality care[12].

The possibility of introducing remote teleconsultations in addition to in-person visits was supported by 62.3% of patients, while 70.4% considered the use of social networks essential for improving disease management both within and outside the hospital. Telemedicine services are currently the subject of studies confirming improved patient access to care, though it remains unclear whether patients are satisfied with telemedicine[13]. Since this service is not currently provided to pediatric or adolescent patients, the data suggest that adolescents would be willing to engage in teleconsultations. Whether these meet their expectations was not investigated. By implementing this service for pediatric hospital patients, future studies could assess whether and to what extent patients are satisfied with telemedicine services. Additionally, such research could determine whether both adolescent patients and their parents appreciate remote visits and follow-ups.

These results indicate that adolescent patients generally perceive the pediatric hospital positively, though there is considerable room for improvement. As noted, perceived quality does not always equate to actual care quality. While the hospital environment was deemed welcoming and appropriate in most areas investigated, certain needs, particularly regarding waiting times and the composition of the follow-up team, were not fully met.

Although this study focuses solely on the care provided to adolescents in a hospital in Bari (Italy), it is reasonable to hypothesize that similar perceptions might exist in other hospitals across Italy. Given the generally uniform nature of the national healthcare system, there are many similarities among hospitals in service delivery. Furthermore, most healthcare professionals receive similar training and are likely to provide comparable standards of care.

CONCLUSIONS

Despite the generally positive feedback obtained from this survey, analyzing adolescent patients' perceptions of the quality of care provided has offered valuable insights for improving the quality of care. Reducing waiting times, providing psychological support, and implementing telemedicine services appear to be key areas for enabling our hospital to become a truly "adolescent-friendly" facility.

Artificial intelligence-assisted technologies:

No artificial intelligence-assisted technologies were used in the production of this article.

Authors' contributions:

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GENOTYPE AND PHENOTYPE OF SUBJECTS WITH TANGIER DISEASE DEVELOPING CARDIOVASCULAR DISEASE

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***ABSTRACT* – Objective:** Tangier Disease (TD) is a rare inherited disorder that disrupts high-density lipoprotein (HDL) metabolism due to loss-of-function variants in the ATP-binding cassette subfamily A member 1 *(ABCA1)* gene. TD patients exhibit diverse clinical presentations, with only some individuals developing cardiovascular disease (CVD) despite extremely low HDL levels. To date, no detailed analyses have explored the genetic and phenotypic markers predicting cardiovascular complications in TD patients. This study aims to identify specific traits distinguishing TD patients prone to CVD.

Materials and Methods: We reviewed all documented TD cases with a genetic diagnosis and constructed a clinical and genetic database using terms from the Human Phenotype Ontology database.

Results: Among 73 TD patients with genetic diagnoses reported in the literature, 30 (41%) experienced CVD, while 43 (59%) did not. Patients with CVD exhibited recurring *ABCA1* variants (n=25), absent in those without complications. These variants also showed distinct distributions across *ABCA1* protein domains (X^2=6.0685, p=0.04). Demographic and clinical features strongly associated with cardiovascular risk included older age (53 ± 10 years *vs.* 45 ± 15 years, p=0.04), orange-colored tonsils (X^2=10.374, p=0.001), and hepatomegaly (X^2=6.423, p=0.01). Lipid profiles and gender differences were not significant between groups.

Conclusions: This study demonstrates, for the first time, that both genetic and phenotypic markers distinguish TD patients with cardiovascular complications. Future research is needed to confirm whether these differences reflect distinct disease mechanisms.

Keywords: Tangier disease, Variants, High-density lipoprotein metabolism, Atherosclerosis.

INTRODUCTION

Tangier disease (TD) (OMIM 205400, ORPHA 31150) is an inborn metabolic disease (IMD) caused by a deficiency in High-Density Lipoprotein (HDL) metabolism[1]. The prevalence of this disease has been estimated at 1:640.000[2].

The disease was first identified in a proband from Tangier Island, located in Chesapeake Bay, (VA, USA), an isolated community that remained geographically secluded for centuries[3].

By the late 1990s, researchers established that TD results from loss-of-function variants in the *ABCA1* gene[4-6]. Individuals carrying homozygous or compound heterozygous loss-of-function variants in *ABCA1* exhibit extremely low HDL levels and an accumulation of cholesteryl and retinyl

esters, along with carotenoids, in non-adipose tissues. Clinically, TD may present with multi-systemic manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, peripheral neuropathy, and corneal opacifications. Cardiovascular disease (CVD) is also observed in some, but not all, patients[7].

Genome-wide studies have identified polymorphisms in *ABCA1* loci as significant determinants of HDL cholesterol levels in the general population[8]. However, whether these common polymorphisms in *ABCA1* associate with altered risk of CVD is less clear.

To date, no analysis has specifically focused on *ABCA1* variants associated with cardiovascular complications in TD patients. Investigating these variants offers a unique opportunity to explore the genetic mechanisms underlying *ABCA1*'s impact on cardiovascular risk, particularly as all identified variants result in a loss of gene function.

Thus, the purpose of this study is to assess the prevalence and localization of *ABCA1* variants, and the clinical phenotypes specifically associated with the cardiovascular complications in all TD subjects reported in the literature.

MATERIALS AND METHODS

Literature Search

We applied the PRISMA methodology in PubMed, Scopus, and Web of Science libraries until September 2024 using the following predefined term: "Tangier Disease". We could retrieve a total of 765 articles. We selected only original articles (568) and, among them, we excluded reports lacking complete and adequate information on clinical and genetics data, which left a total of 100 papers available for this review (**Supplementary Figure 1**).

TD Subject Database Creation

We collected from the literature all the cases of TD (n=128) with a reported genetic cause of the disease, and we built the clinical and genetic database using the terms associated with TD in the Human Phenotype Ontology database.

Among the included cases, a specific description of the presence or not of a CVD, defined as carotid artery stenosis or accelerated atherosclerosis or coronary artery stenosis or left ventricular hypertrophy, was reported in 73 cases.

Statistical Analysis

Frequency of categorical variables was analyzed with Pearson's χ^2. Quantitative variables were compared using T-test. Significance was set at p<5*10-2. SPSS for Mac (vers. 29 for Mac, IBM-SPSS Bologna, Italy) and GraphPad, Prism (vers. 8.1.3 for Mac, GraphPad Software, La Jolla, CA, USA) were used for the statistical analyses.

RESULTS

Variants of ABCA1 associated with cardiovascular manifestations in TD cases

Among the 128 cases that we collected from the literature, a total of 79 different genotypes were identified. The most frequent were c.1764delG (6 cases), c.2033C>A (4), c.5094C>A, and c.219insT (3 cases), respectively. In 67% of patients the disease was caused by a homozygous variant and homozygous subjects were significantly younger (p=0.016). Among them, 45% of cases (n=30) developed a CVD and 23% (n=15) died after it. By selecting only subjects with a CVD, we found 31 variants of *ABCA1* gene,

of which 25 known to cause a change in the protein-coding sequence (Table 1 and Figure 1, panel A). Most of them were specifically associated with the CV phenotype: only 6 variants (p.N935H, p.H1600R, p.R1270X, p.R587A, p.W1699C, p.Y1698X) were detected in patients with or without a CVD. All published cases carrying the homozygous c.1764delG (p.L548X) variant suffered from a CVD. In particular, this variant appears specifically associated with CVD since it was not reported in patients who did not develop a CVD.

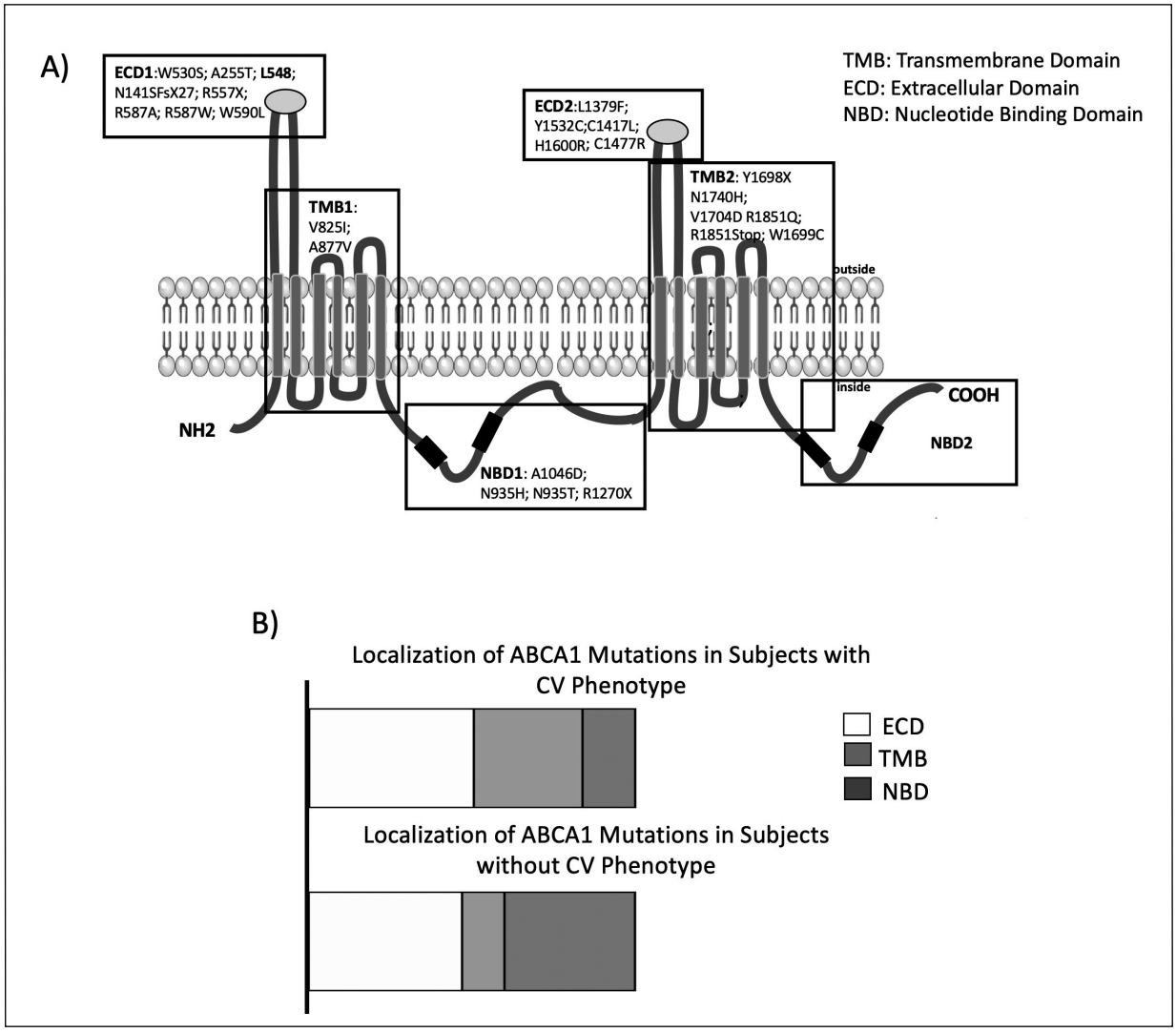

Figure 1. Localization of the ABCA1 variants associated with CV disease in TD subjects. The majority of ABCA1 variants in TD cases with CV phenotype occurs in the large extracellular loops, while the areas where ATP is hydrolysed (NBDs) are apparently the less mutated in subjects with CV disease (Panel A). Comparison of the variant localization on ABCA1 protein domains associated with (Panel B, upper) or without CV disease (Panel B, bottom).

Functional mapping of ABCA1 variant associated with cardiovascular manifestations in TD cases

To understand whether variants associated with the CV phenotype specifically map on functional regions of *ABCA1*, we assessed their distribution on the different *ABCA1* protein domains.

ABCA1 is composed of two transmembrane domains (TMDs), two nucleotide-binding domains (NBDs), and two extracellular domains (ECDs)[9]. The two large extracellular domains are responsible for the binding of apo A-I[8], the two nucleotide-binding domains function as ATP hydrolases providing the energy for substrate transport and the two large transmembrane domains (TMDs) contain the substrate-binding site[10].

Table 1. Variants of *ABCA1* associated with CV disease in TD subjects.

Aminoacid Change	DNA Change
A1046D	C3137A
A255T	G1158A
A877V	C2750T
C1417L	T4369C
C1477R	G3738C
H1600R	1758_1759 insGA4799G
L1379F	C4425T
L548	G1764
N141SFsX27	NA
N1740H	A5338C
N935H	A3198C
N935T	A3198G
R1270X	C3808T
R1851Q	G5947A
R1851Stop	C5946T
R557X	NA
R587A	1758_1759insG
R587W	C1699T
V1704D	T5401A
V825I	NA
W1699C	A5097G
W530S	G1709C
W590L	NA
Y1532C	A4595G
Y1698X	C5094A

Of all published *ABCA1* variants reported in TD cases with a CVD, 50% mapped in the extracellular domain (ECD1 and 2) regions, with a 33% in ECD1 and 17% in ECD2, respectively (Figure 1 Panels A and B). A total of 34% mapped on the transmembrane domains (9% on TMB1 and 25% on TMB2); 16% were on the nucleotide-binding domain 1 (NBD1) and no variant on the NBD2 (C-term).

Looking at the distribution of the variants detected in subjects who did not develop a CVD, the extracellular distribution rate is maintained (30% in ECD1 and 17% in ECD2), while, intracellularly, the rate in NBD1 (33%) and NBD2 (7%) increases to 40%, and in TMB1 and 2 decreases to 13% (0% and 13%, respectively) (Figure 1 Panel B). The localization pattern of variants was significantly different between subjects with and without a CVD (X^2=6.0685, p=0.048).

Other factors associated with cardiovascular manifestations in TD cases

To understand whether other features may be able to distinguish TD cases with or without a CVD, we compared clinical and demographics characteristics of the subject included in the study.

By this analysis, we found that the group of patients with CVD was older (53±10y) than the non-CVD patients (45±15y, p=0.04). Considering the multi systemic manifestations of the disease (Table 2) and comparing subjects with or without CVD, we found that the presence of CVD is associated with the

Table 2. The Human Phenotype Ontology terms associated or not to cardiovascular manifestations in TD patients.

HPO_TERM_NAME	Category	Association with Cardiovascular Phenotype
Anemia	Blood and blood-forming tissues	Yes
Thrombocytopenia	Blood and blood-forming tissues	Yes
Hepatosplenomegaly	Digestive System	Yes
Chronic noninfectious lymphadenopathy	Immunology	Yes
Orange discolored tonsils	Immunology	Yes
Hypertriglyceridemia	Metabolism/Laboratory abnormality	No
Hypocholesterolemia	Metabolism/Laboratory abnormality	No
Impaired thermal sensitivity	Constitutional Symptom	NA*
Abdominal pain	Constitutional Symptom	No
Corneal opacity	Eye	Yes
Ectropion	Head and neck	NA*
Distal muscle weakness	Musculature	NA*
Facial diplegia	Musculature	NA*
Syringomyelia	Nervous System	No
Peripheral axonal neuropathy	Nervous System	No
Progressive peripheral neuropathy	Nervous System	No
Nail dystrophy	Skin, Hair, and Nails	No
Dry skin	Skin, Hair, and Nails	No

*Data not available in analyzed TD subjects.

presence of orange discoloured tonsils (X^2=10.374, p=0.001), splenomegaly (X^2=3.923, p=0.04), hepatomegaly (X^2=6.423, p=0.01), corneal opacity (X^2=4.861, p=0.03), anemia (X^2=7.875, p=0.02) and thrombocytopenia (X^2=5.185, p=0.03) (Table 1).

On the other hand, the lipid profile (LDL, HDL, Total Cholesterol, and Triglycerides) of cases with or without CVD was not different (Table 3). Data on cholesterol efflux of primary fibroblasts were reported only in 12 cases (6 with CVD and 6 without), thus we did not consider them in the statistical analysis.

No association was found with CVD and the presence of homozygous or compound heterozygous variants, the patient's gender, and neurological manifestations.

Table 3. Lipid profile of TD patients with or without CV disease.

	Without CVD (n=33)	With CVD (n=25)
Total Cholesterol (mg/dl)	83.5 ± 32.8	85.6 ± 39.8
HDL (mg/dl)	3.4 ± 2.0	3.1 ± 1.9
Triglycerides (mg/ml)	216.2 ± 185.0	206.9 ± 100.6
LDL (mg/dl)	62.0 ± 37.1	66.0 ± 37.1

DISCUSSION

The investigation of TD provides profound insights into the critical role of the *ABCA1* in cholesterol metabolism and cardiovascular health.

ABCA1 protein facilitates the transfer of cholesterol and phospholipids from peripheral cells, such as macrophages, to lipid-poor apolipoprotein A-I (apoA-I)[11]. This step is vital for the formation of nascent HDL particles[12]. In TD, defective or absent *ABCA1* function disrupts this process, leading to the intracellular accumulation of cholesterol and lipids in peripheral tissues[13]. The absence of functional HDL in TD leaves excess cholesterol stranded in the arterial wall, fostering an environment conducive to atherogenesis[14]. Moreover, HDL deficiency eliminates its systemic protective roles, amplifying the risk of cardiovascular complications.

However, even if early studies on TD, patients reported a high incidence of CVD[4-6], when more cases were observed globally, it became evident that the clinical manifestations of TD are highly variable, ranging from neurological symptoms to cardiovascular complications.

In this study, we identified recurrent variants in 45% of TD patients who developed CVD (**Figure 1**). Notably, the p.L548X variant is the most common, found in 20% of CVD patients. Originally described by Rust et al[6] in 1999, this variant was discovered in a German family with premature CVD onset. The variant, a 1-bp deletion in exon 13 (c.1764delG), results in a stop codon that eliminates most of the *ABCA1* protein sequence, including both ATP-binding cassettes.

Further studies comparing fibroblasts from two TD patients – one with the p.L548X variant and another with a p.N935S variant not associated with CVD – revealed significantly lower cholesterol efflux capacity in p.L548X cells. This finding suggests that variants like p.L548X, which severely impair protein function, may be linked to the development of CVD.

Another case study identified a 20% difference in cholesterol efflux capacity between fibroblasts from patients with differing cardiovascular phenotypes and *ABCA1* variants. One subject, who had a severe CVD phenotype, carried a missense variant (p.C1477R), whereas another, without atherosclerosis, harbored a nonsense variant (GG5277,8C) and a *de novo* missense variant (p.T929I). These findings suggest that more severe *ABCA1* variants are likely associated with cardiovascular complications. We hypothesized that recurrent variants in subjects with CVD could disrupt a specific function of *ABCA1*, possibly its interaction with apoA-I or ATPase activity. Since functional domains of *ABCA1* are well-characterized, we analyzed the location of variants on these domains.

Our analysis confirmed that most variants occurred in the large extracellular loops responsible for apoA-I binding, consistent with previous reports on TD patients. However, for the first time, we observed that variants in Transmembrane Binding Domains (TMBs), which regulate substrate transport, were more common in patients with CVD, whereas variants in Nucleotide Binding Domains (NBDs), which function as ATP hydrolases, were more frequent in subjects without CVD.

In addition to genetic findings, we identified specific multi-systemic manifestations associated with CVD, such as orange discolored tonsils, splenomegaly, hepatomegaly, corneal opacity, anemia, and thrombocytopenia. Interestingly, these traits were not linked to the neurological manifestations often seen in TD patients, suggesting two distinct subgroups: one prone to cardiovascular issues with mild neurological symptoms, and another with more severe neurological involvement but without CVD.

Surprisingly, no differences were found in lipid profiles (LDL, HDL, total cholesterol, and triglycerides) or other demographic features, except for age. This discrepancy suggests that the relationship between lipid levels and cardiovascular risk in TD is more complex than previously thought. Factors like environmental influences and the multi-step process of atherosclerosis may obscure the role of HDL levels in CVD risk. More research, particularly cellular models, is needed to clarify this relationship and assess the full risk profile for TD patients.

CONCLUSIONS

Our results indicate that the type and location of *ABCA1* variants play a key role in the molecular mechanisms leading to specific complications in TD. This finding could have significant implications for understanding the pathogenesis of TD and for guiding the genetic evaluation and clinical management of patients.

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LL and NV conceived and wrote the manuscript; ST extracted data from literature; AA revised the manuscript.

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CHANGES IN THE CARE OF PATIENTS WITH LYSOSOMAL STORAGE DISEASES IN THE POST-COVID-19 ERA

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***ABSTRACT* – Objective:** The aim of this study is to assess the extent of changes in the care of patients with lysosomal storage disorders (LSDs) during the COVID-19 pandemic and to determine which of these changes have been maintained in the post-COVID-19 era.

Patients And Methods: Data were analyzed from a single large Reference Center for Lysosomal Storage Diseases (the Regional Coordinating Center for Rare Diseases in Udine, Italy). Changes in patient care were assessed by comparing the pre-pandemic period (December 2019) with the post-pandemic period (December 2023), focusing on the proportion of patients who transitioned to home therapy and the use of telemedicine consultations.

Results: A total of 102 patients with LSDs followed at the Regional Coordinating Center for Rare Diseases were included in the analysis. Before the pandemic, 71 patients were receiving enzyme replacement therapy (ERT), with 55 treated in the hospital and 16 at home. During the pandemic, an additional 15 patients transitioned to home-based ERT, and only 2 later resumed hospital-based infusions. No adverse events were reported in the home setting. Telemedicine services were utilized by 53 out of 102 patients during the pandemic and by 47 out of 102 patients in the post-pandemic period.

Conclusions: The COVID-19 pandemic led to changes in the management of patients with LSDs, including an increase in home therapy and the implementation of telemedicine services. These changes have persisted in the post-COVID-19 era.

Keywords: LSD, ERT, Home therapy, Telehealth, COVID-19.

List of abbreviations: AIFA – Italian Medicines Agency; CCRMR – Regional Coordinating Center for Rare Diseases; CCRMR-FVG – Regional Coordinating Center for Rare Diseases of Friuli Venezia Giulia; COVID-19 – Coronavirus Disease 2019; ERT – Enzyme Replacement Therapy; HomeERT – Home-based Enzyme Replacement Therapy; LSD – Lysosomal Storage Disease; LSDs – Lysosomal Storage Diseases; WHO – World Health Organization.

INTRODUCTION

Lysosomal storage diseases (LSDs) are a heterogeneous group of inherited metabolic disorders that affect multiple organs and systems, with an estimated overall prevalence of approximately 1 in 5,000 live births[1]. These rare genetic disorders are characterized by the accumulation of toxic substances within lysosomes due to the absence or dysfunction of specific enzymes responsible for their degradation. This accumulation can lead to systemic involvement and, in some cases, premature death[2]. Although LSDs are rare, their clinical and social implications are significant, particularly due to the need for highly specialized, multidisciplinary medical care and regular monitoring. For some LSDs, targeted therapies

are available, requiring consistent administration to ensure their effectiveness. These include enzyme replacement therapy (ERT), administered intravenously, as well as oral treatments such as substrate reduction therapy and chaperone drugs[3].

In 2020, the global health emergency caused by the coronavirus (COVID-19) pandemic, driven by the SARS-CoV-2 virus, had a profound impact on healthcare systems worldwide. This was particularly evident during the early stages of the pandemic, as it disrupted healthcare delivery models and posed unprecedented challenges for patients with chronic diseases, including LSDs[4]. For these patients, the transition from hospital-based ERT to home therapy, along with the implementation of telemedicine, served as crucial strategies to ensure continuity of care while simultaneously reducing the risk of infection in healthcare settings[5,6].

The shift in healthcare services toward telemedicine and home therapy may persist in the post-COVID-19 era[7]. However, to date, no studies have analyzed which changes in the management of LSDs induced by the COVID-19 pandemic have been maintained in the post-pandemic period.

The aim of this study was to assess the extent of these changes from the pre-COVID-19 to the post-COVID-19 period by analyzing data from a large Reference Center for LSDs.

PATIENTS AND METHODS

A retrospective analysis was conducted on the care processes at the Regional Coordinating Center for Rare Diseases of Friuli Venezia Giulia (CCRMR-FVG) in Udine, Italy, covering the period from December 2019 to December 2023. The analysis included all adult patients with a confirmed diagnosis of LSD who were continuously followed at the center and were on a specific treatment, excluding those on clinical trials.

The pre-pandemic reference period was defined as December 2019. Changes occurring during the pandemic were considered from March 11, 2020, to May 5, 2023, in accordance with the World Health Organization's definition of the COVID-19 pandemic period[8]. The post-pandemic period was defined as December 2023.

The analysis aimed to address the following questions:

1. Which proportion of patients experienced modifications to their usual enzyme replacement therapy (ERT) regimen, specifically transitioning to home therapy during the pandemic?
2. Which proportion of patients resumed hospital-based infusions after the pandemic?
3. Which proportion of patients utilized telemedicine services, including medical or psychological consultations, before, during, and after the pandemic?

Data were extracted from the hospital's electronic clinical system with prior patient consent. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study has been approved by the Local Ethical Committee – CEUR FVG Prot. N. 860.

Statistical analysis

A descriptive statistical analysis was performed. Data were reported as absolute numbers and percentages.

RESULTS

A total of 102 patients with LSDs followed at the Regional Coordinating Center for Rare Diseases were included in the analysis. The distribution of diseases was as follows: Gaucher disease (44 patients; 39 with type I, 5 with type III), Pompe disease (16 patients), Fabry disease (15 patients), mucopolysaccharidoses (12 patients; 3 with type I, 5 with type II, 1 with type IV, 3 with type VI), Niemann-Pick disease type C (10 patients), and cystinosis (5 patients). More details on general characteristics of patients have been included in Table 1.

In December 2019, 71 patients (69.6%) were receiving ERT with imiglucerase, velaglucerase, laronidase, galsulfase, idursulfase, elosulfase alpha, alglucosidase alpha, or alpha and beta galactosidase. Among these, 55 patients (77.5%) received treatment in the hospital, while 16 (22.5%) underwent home therapy.

Table 1. General characteristics of patients.

	Frequency	Percentage
Sex		
• Female	49	48.04%
• Male	53	51.96%
Disease		
• Cystinosis	5	4.90%
• Fabry	15	14.71%
• Gaucher I	39	38.24%
• Gaucher III	5	4.90%
• MPS I	3	2.94%
• MPS II	5	4.90%
• MPS IV	1	0.98%
• MPS VI	3	2.94%
• Niemann Pick C	10	9.80%
• Pompe	16	15.69%
Age (years)		
• *n*=102 patients	Range: 18–87 years	Mean ± SD: 38.8 ± 18.6

During the pandemic years, no patients transitioned from home therapy to hospital-based treatment, whereas 15 patients (27.3% of those previously receiving ERT in the hospital) switched to home-based ERT. Consequently, the number of patients on home therapy nearly doubled (+93%).

By December 2023, only two of these patients had resumed hospital-based infusions in the post-pandemic period, both due to logistical issues related to the unavailability of home-care nurses in their respective areas. As a result, home-based ERT was maintained in 86.6% of cases (Figure 1). No adverse events were reported in the home setting.

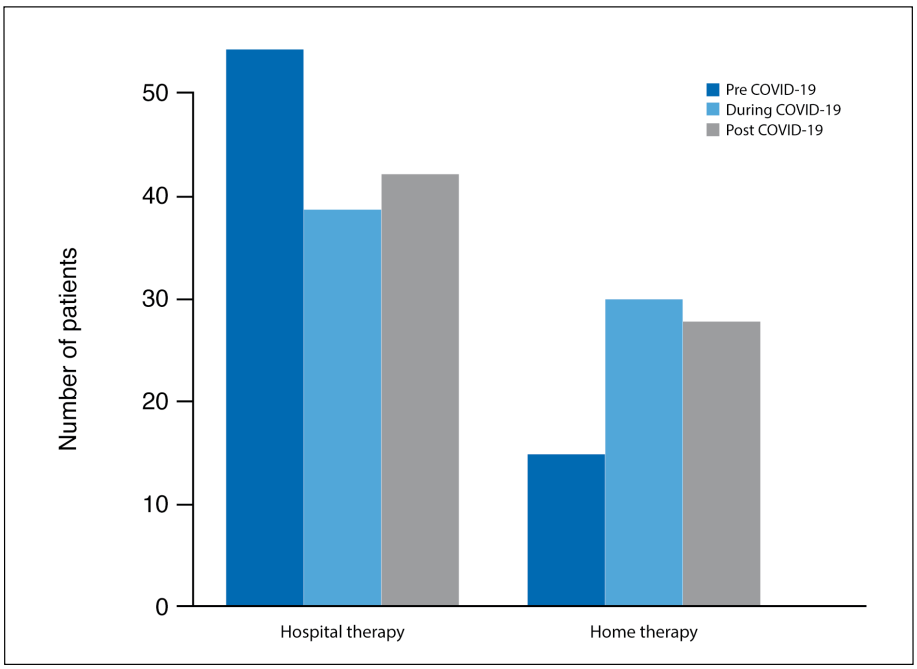

Figure 1. Changes in the administration setting of enzyme replacement therapy from the pre-pandemic to the post-pandemic period.

Regarding telemedicine, no patients utilized teleconsultation services before the pandemic, as this service was not available at the Regional Coordinating Center for Rare Diseases. During the pandemic years, 53 patients (52% of the total LSD cohort) accessed telemedicine services. In the post-pandemic period, 47 patients continued to use telemedicine (Figure 2).

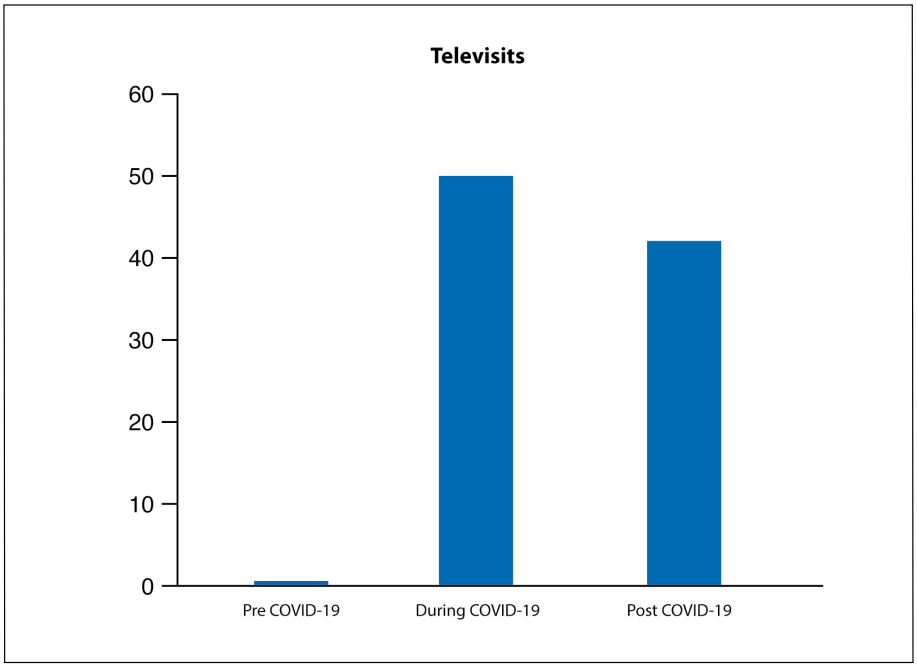

Figure 2. Number of patients who utilized telemedicine services from the pre-pandemic to the post-pandemic period.

DISCUSSION

The COVID-19 pandemic placed significant strain on healthcare systems worldwide. During this period, social distancing measures, temporary closures of healthcare facilities, and the reallocation of resources affected medical care and patient management to varying degrees. For patients with LSDs, the necessity of attending hospitals for essential treatments conflicted with concerns – shared by both patients and healthcare professionals – about the risk of COVID-19 infection[9].

ERT, which delivers the deficient enzyme through regular infusions, is often the only specific treatment available for LSDs. Missing multiple infusions can lead to complications, including symptom exacerbation, disease progression, and an increased risk of adverse drug reactions upon resumption of treatment. With the spread of COVID-19, hospitals became potential hotspots for infection, posing a particular risk to vulnerable patients, such as those with LSDs[10]. As a result, many patients initially chose to forgo scheduled hospital infusions, even at the expense of their health. This highlighted the need for more flexible therapeutic strategies, including alternative routes and settings for drug administration. Consequently, changes in treatment management were implemented, such as transitioning to home therapy or switching from intravenous to oral therapy where available and clinically appropriate[5]. In the early stages of the pandemic (April 2020), the Regional Coordinating Center for Rare Diseases of Friuli Venezia Giulia (CCRMR-FVG) conducted a survey among its LSD patients, revealing that 49% of those receiving hospital-based ERT experienced treatment interruptions. The primary reasons were fear of infection (62.9%), and logistical challenges related to the reorganization of infusion centers (37%). In contrast, only 6% of patients on home therapy experienced treatment interruptions[5]. In March 2020, the Italian Medicines Agency (AIFA) issued Resolution 341/2020, allowing a broader implementation of home therapy for LSD patients. This resolution also enabled home-based ERT for patients with Pompe disease, a treatment option that had previously not been permitted in Italy.

Our data indicate a 93% increase in the number of patients receiving home-based ERT during the pandemic, with 86.6% of these patients continuing home therapy in the post-pandemic period. No adverse events were reported in the home setting, a finding consistent with previous studies on home

therapy[11-13]. Despite its numerous advantages for patients – including reduced impact on daily activities, decreased travel time, and lower perceived stress[14] – home therapy remains unavailable in many countries. Even within Italy, access to home-based ERT varies across different regions.

The implementation of telemedicine emerged as a key resilience strategy during the COVID-19 pandemic. By enabling remote consultations, patients with chronic diseases, including LSDs, were able to receive prescriptions, medical advice, and follow-up care without the need to visit healthcare facilities, thereby reducing the risk of infection[15].

Although telemedicine was not a new concept, its use expanded significantly during the pandemic, profoundly transforming healthcare delivery. This approach not only allowed patients and physicians to interact safely and effectively during the COVID-19 crisis[16] but also facilitated continued patient-provider communication in the post-pandemic period.

Studies on LSD patients during the COVID-19 pandemic highlighted the negative impact of the pandemic on mental health[17]. In response, the Regional Coordinating Center for Rare Diseases (CCRMR) expanded its telemedicine services to include psychological consultations.

CCRMR data indicate that while telemedicine utilization surged during the pandemic, it has been retained in the post-COVID-19 era, not as a replacement for in-person visits but as an integrated component of patient care. This hybrid approach allows for more frequent and flexible interactions between patients and healthcare providers, even remotely.

Limitations

The primary limitation of this analysis is that it was conducted at a single center. While the Regional Coordinating Center for Rare Diseases (CCRMR) serves as a valuable model due to its large cohort of LSD patients, certain center-specific characteristics may have influenced the findings. Notably, approximately 80% of patients followed at the CCRMR reside outside the region. This may have contributed to the high proportion of patients who continued using telemedicine in the post-COVID-19 period. Additionally, the CCRMR was one of the first centers in Italy to implement clinically and institutionally recognized teleconsultations, including both medical and psychological visits, with formal documentation. The large number of out-of-region patients may have also impacted the transition to home-based ERT, as the feasibility of home therapy depended on regional healthcare policies, which varied based on the patient's place of residence. Another major limitation of this study is its reliance on purely numerical data, lacking qualitative patient feedback. Consequently, it remains unclear whether patients perceived these changes positively and whether they had a meaningful impact on their disease experience and quality of life.

A patient-reported outcome questionnaire assessing the qualitative aspects of HomeERT and telemedicine is currently being validated, which may support future multicenter studies. Other indicators of efficacy of home-infusion and telemedicine can be subject of these future studies, including numbers of missed infusions at home compared to hospital, number of contacts for telemedicine, type of interventions, and eventual coordination with general practitioners.

CONCLUSIONS

The COVID-19 pandemic led to potentially beneficial changes in the management of patients with LSDs, including the transition to home-based ERT and the integration of traditional healthcare with telemedicine. These changes have been maintained in the post-COVID-19 era. Further studies involving a larger number of centers and incorporating patient perspectives are needed to better assess the actual impact of these changes on clinical practice and patient quality of life.

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Study conception and design: Paola Piovani; collection and interpretation of data: all authors; statistical analysis: Paola Piovani; manuscript drafting: Paola Piovani, Martina Bon; manuscript editing: Paola Piovani, Martina Bon; approval to submit: all authors.

Availability of data and material:

The datasets generated or analyzed during the current study are not publicly available due to the nature of the analysis but are available from the corresponding author on reasonable request.

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The authors declare that they have no conflict of interest to disclose.

Ethics approval:

This study has been approved by the Local Ethical Committee – CEUR FVG Prot. N. 860.

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All patients involved in the study signed an informed consent for “Dossier Sanitario Elettronico”.

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A MULTIDISCIPLINARY BIOCHEMICAL AND GENETIC APPROACH FOR THE DIAGNOSIS OF CONGENITAL ADRENAL HYPERPLASIA: A PEDIATRIC CASE

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***ABSTRACT* – Objective:** This study aimed to demonstrate the potential of integrating genetic and biochemical approaches for the rapid and definitive diagnosis of congenital adrenal hyperplasia.

Case presentation: We report the case of a 5-year-old boy presenting with early puberty and significantly advanced bone age. Due to a strong suspicion of congenital adrenal hyperplasia, the patient underwent diagnostic evaluation incorporating both biochemical and genetic analyses.

Results: Biochemical analysis using ultra-performance liquid chromatography–tandem mass spectrometry revealed a marked accumulation of 17-hydroxyprogesterone, with the steroid profile confirming a pattern characteristic of 21-hydroxylase deficiency. Sanger sequencing identified the pathogenic variant c.515T>A (exon 4) in a heterozygous state, while multiplex ligation-dependent probe amplification detected a heterozygous deletion of exons 1, 3, 4, 6 and 7 in the *CYP21A2* gene. Parental segregation analysis showed that the c.515T>A variant was inherited from the father, whereas the large heterozygous deletion originated from the mother.

Conclusions: A multidisciplinary approach integrating biochemical and genetic analyses enables a definitive and early diagnosis of congenital adrenal hyperplasia, facilitating appropriate treatment and preventing serious or fatal complications associated with the classic form of the disease.

Keywords: Congenital Adrenal Hyperplasia, 17-hydroxyprogesterone, Deletion.

List of abbreviations: 4-A: 4-androstene-3,17-dione; 11-DC: 11-deoxycortisol; 17-OHP: 17-hydroxyprogesterone; 21-OHD: 21-hydroxylase deficiency; ACTH: adrenocorticotropic hormone; CAH: Congenital Adrenal Hyperplasia; CORT: cortisol; DBS: dried blood spot; LC-MS/MS: liquid chromatography with tandem mass spectrometry; MLPA: multiplex ligation-dependent probe amplification; SV: Simple Virilizing; SW: Salt-Wasting; UPLC-MS/MS: ultra-performance liquid chromatography with tandem mass spectrometry.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a monogenic autosomal recessive disorder caused by defective adrenal steroid hormone synthesis due to enzyme deficiencies or malfunctions in the steroidogenic pathway[1].

Steroid 21-hydroxylase deficiency (21-OHD) is the most common cause of CAH, accounting for at least 90% of cases[2,3]; however, other enzymes in the same biochemical pathway may also be implicated (Table 1)[4].

Table 1. Biochemical pathways involved in different forms of CAH.

Percentage of CAH	Deficient Enzyme	Substrate	Product	Androgen	Mineralo-corticoid
Unknown	Steroidogenic acute regulatory protein	–	Mediates cholesterol transport across the mitochondrial membrane	Deficiency	Deficiency
Unknown	3β-hydroxysteroid-dehydrogenase	Pregnenolone,17-OH pregnenolone, Dehydroepian-drosterone	Progesterone, 17-OHP,Δ -androstenedione	Deficiency	Deficiency
Unknown	17α-hydroxylase	Pregnenolone Progesterone	17-OH pregnenolone 17-OH (17-OHP)	Deficiency	Excess
>90%	21-hydroxylase	Progesterone 17-hydroxy progesterone	Deoxycorticosterone 11-deoxycortisol	Excess	Deficiency
5%	11β-hydroxylase	Deoxycorticosterone	Corticosterone	Excess	Excess

Abbreviations – 17-OH: 17-hydroxy; 11-DC: 11-deoxycortisol; 17-OHP: 17-hydroxyprogesterone; 21-OHD: 21-hydroxylase deficiency. Source: Nimkarn et al[5]. Reproduced with permission from GeneReviews® (© 1993-2025 University of Washington).

The *CYP21A2* gene encodes the 21-hydroxylase enzyme, and point mutations, deletions/duplications, or gene conversions involving its highly homologous pseudogene (*CYP21A1P*) can result in enzyme deficiency or dysfunction, leading to CAH with variable clinical phenotypes (**Table S1**).

The disease exhibits a wide spectrum of clinical severity (Table 2). The classic form presents prenatally with severe enzyme deficiency and is further classified into the salt-wasting (SW) and simple virilizing (SV)

Table 2. Mean levels and range of response of paternal engagement.

Enzyme activity	Phenotype	CYP21A2 pathogenic variant
0%	Severe (classic)	• Whole-gene deletion (null variant) • Large-gene conversion • p.Gly111ValfsTer21 • p.[Ile237Asn;Val238Glu;Met240Lys] • p.Leu308PhefsTer6 • p.Gln319Ter • p.Arg357Trp
<1%1		• c.293-13A>G • c.293C>G
2–11%		• p.Ile173Asn
~20–50%	Mild (non-classic)	• p.Pro31Leu • p.Val282Leu • p.Pro454Ser

Source: Nimkarn et al5. Reproduced with permission from GeneReviews® (© 1993-2025 University of Washington).

subtypes. The most severe SW form affects approximately 25% of individuals and is characterized by adrenal insufficiency, often leading to hypovolemic shock, hyponatremia, hyperkalemia, metabolic acidosis, and, in some cases, hypoglycemia. The less severe SV form accounts for ≥75% of affected individuals and is typically associated with hyperandrogenism, premature adrenarche/puberty, apocrine odor, clitoromegaly, rapid growth and accelerated skeletal maturation, which may compromise final height[1,5].

The non-classic (NC) form has a postnatal onset and is associated with the mildest enzyme deficiency. The most common reason for medical consultation in these patients is late-onset hyperandrogenism, which typically manifests during the peri-pubertal stage or adulthood. In adolescence, frequent clinical concerns include acne, hirsutism, and oligomenorrhea, a condition that may be clinically indistinguishable from polycystic ovary syndrome. Some affected individuals also exhibit polycystic ovarian morphology[6].

The initial diagnosis of CAH is typically based on plasma 17-hydroxyprogesterone (17-OHP) levels. Measurement techniques include immunoassays and liquid chromatography–tandem mass spectrometry (LC-MS/MS). In borderline cases, an adrenocorticotropic hormone (ACTH) stimulation test (250 µg intramuscularly or intravenously) is recommended to confirm the diagnosis. In our laboratory, for LC-MS/MS plasma measurements, 17-OHP reference range in pediatric population are 0.03–2.65 ng/mL.

When classic CAH is suspected, additional adrenal steroids, including cortisol, aldosterone, androstenedione, and dehydroepiandrosterone sulfate, should be assessed. The mineralocorticoid axis should also be evaluated by measuring plasma renin and plasma electrolytes. Genetic testing is strongly recommended for all cases in which biochemical findings suggest CAH and is particularly valuable for confirming the diagnosis in complex cases[6].

For molecular analysis, Sanger sequencing combined with multiplex ligation-dependent probe amplification (MLPA) is commonly used in many laboratories to detect single nucleotide variations, small insertions/deletions (indels), and large deletions/duplications in the *CYP21A2* gene[7,8].

The combination of biochemical and genetic analyses is essential for an accurate and rapid diagnosis of CAH. In this study, we report a case with a high suspicion of CAH to demonstrate the potential of integrating genetic and biochemical approaches for a definitive and early diagnosis. Furthermore, parental segregation analysis proved useful in refining the patient's genotype and determining the specific CAH subtype.

MATERIALS AND METHODS

Genetic and biochemical analyses were performed using peripheral blood and dried blood spot (DBS) samples collected from the patient and parents at the Pediatric Clinic of *SS. Annunziata* Hospital in Chieti, Italy.

DBS samples were analyzed using an ultra-performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS) system to evaluate blood levels of cortisol (CORT), 21-deoxycortisol, 11-deoxycortisol (11-DC), 4-androstene-3, 17-dione (4-A), and 17-OHP[9]. Additionally, the plasma steroid profile was quantified by UPLC-MS/MS, measuring CORT, 11-DC, 4-A, 17-OHP, testosterone, progesterone, corticosterone, and aldosterone using the CHS™ MSMS Steroids Kit (Revvity®, Turku, Finland). The details for quantitative determination in the plasma samples of steroid profile by UPLC-MS/MS are fully described in **Supplementary Materials** and specifically reported in **Tables S2–S3**. The diagnosis of CAH was confirmed through genetic analysis. Genomic DNA was extracted from peripheral blood using the MagPurix instrument and the Whole Blood DNA Extraction Kit (Zinexts Life Science Corp., Ref: ZP01001, New Taipei City, Taiwan) following the manufacturer's protocol. Sanger sequencing and MLPA were employed to identify point mutations within the *CYP21A2* gene and large rearrangements involving *CYP21A2* and its pseudogene, *CYP21A1P*. Sanger sequencing was conducted using the BigDye™ Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Waltham, MA, USA) and the SeqStudio™ Genetic Analyzer System (Thermo Fisher Scientific, Waltham, MA, USA). MLPA was performed using the SALSA® MLPA® probemix P050-D1 CAH kit (MRC-Holland, Amsterdam, The Netherlands) and analyzed on a 3500 Series Genetic Analyzer (Applied Biosystems, Foster City, MA, USA). Copy number variations in *CYP21A2* exons 1, 3, 4, 6 and 7 were assessed using Coffalyser® software (MRC-Holland, Amsterdam, The Netherlands).

This case report does not require an Ethics Committee approval, as per national law. Written informed consents were obtained from parents to perform procedures and describe the case in the literature.

Case Presentation

We report the case of a 5-year-old male proband presenting with early puberty (P3G3, testicular volume: 3 mL) and significantly advanced bone age of 10 years, as assessed by the Greulich-Pyle method. At the time of his initial evaluation, the proband's height was 125.2 cm, weight 35 kg, and BMI 22.3 kg/m². To assess the hypothalamic-pituitary-gonadal axis, a luteinizing hormone-releasing hormone stimulation test was performed, revealing follicle-stimulating hormone and luteinizing hormone (LH) levels of 2.4 mUI/mL and 4.3 mUI/mL at 60 minutes, respectively, with an LH/follicle-stimulating hormone ratio favoring LH (**Table S4**). Serum 17β-estradiol was undetectable (<10 pg/mL), while testosterone and prolactin levels were 1.19 ng/mL and 21.6 ng/mL, respectively. Further endocrine evaluation showed elevated ACTH and dehydroepiandrosterone sulfate levels (52.4 pg/mL and 58 pg/mL, respectively), both exceeding the normal range for age and sex. Additionally, ACTH stimulation test revealed markedly increased baseline 17-OHP levels (>20 ng/mL) and a decrease in cortisol, with no significant increment post-stimulation (**Table S5**). Plasma renin activity was also elevated (168.3 µU/mL). A complete blood count, as well as liver, renal, and thyroid function tests, were within normal limits for age. These findings strongly suggested CAH, consistent with the non-classic form of 21-OHD.

Biochemical and genetic analyses were conducted in our laboratory. The biochemical evaluation revealed a marked accumulation of 17-OHP, and the steroid profile confirmed the diagnosis of CAH with a pattern characteristic of 21-OHD. The DBS and plasma steroid concentrations of the patient are presented in Tables 3 and 4, respectively. For molecular analysis, Sanger sequencing identified the pathogenic variant c.515T>A in exon 4 of the *CYP21A2* gene in a homozygous state, suggesting an SV form of CAH (Figure 1A). MLPA analysis detected a heterozygous deletion of exons 1, 3, 4, 6, and 7 in *CYP21A2* (Figure 1B).

Table 3. Dried blood spot steroid concentrations of analytes and the related cut-offs to which our laboratory refers, based on a neonatal population.

Analyte	Value	Cut-off
17-OHP	84.39 ng/mL	3.60 ng/mL
11-deoxycortisol	0.21 ng/mL	7.65 ng/mL
21-deoxycortisol	8.91 ng/mL	1.80 ng/mL
4-A	3.52 ng/mL	–
Cortisol	10.51 ng/mL	–
(17OHP+4A)/cortisol	8.63 ng/mL	1.00 ng/mL

Abbreviations – 4-A: 4-androstene-3,17-dione; 11-DC: 11-deoxycortisol; 17-OHP: 17-hydroxyprogesterone.

Table 4. Plasma steroid concentrations of analytes and the related cut-offs to which our laboratory refers, based on a pediatric population.

Analyte	Value	Cut-off
17-OHP	149.96 ng/mL	0.03–2.65 ng/mL
11-deoxycortisol	0.32 ng/mL	0.10–1.56 ng/mL
4-A	4.18 ng/mL	0.06–2.60ng/mL
Cortisol	22.45 ng/mL	10–330 ng/mL
Testosterone	1.37 ng/mL	0.03–9.70 ng/mL
Progesterone	4.88 ng/mL	0.07–12.94 ng/mL
Corticosterone	1.78 ng/mL	0.80–18.60 ng/mL
Aldosterone	0.30 ng/mL	0.05–0.90 ng/mL

Abbreviations – 4-A: 4-androstene-3,17-dione; 11-DC: 11-deoxycortisol; 17-OHP: 17-hydroxyprogesterone.

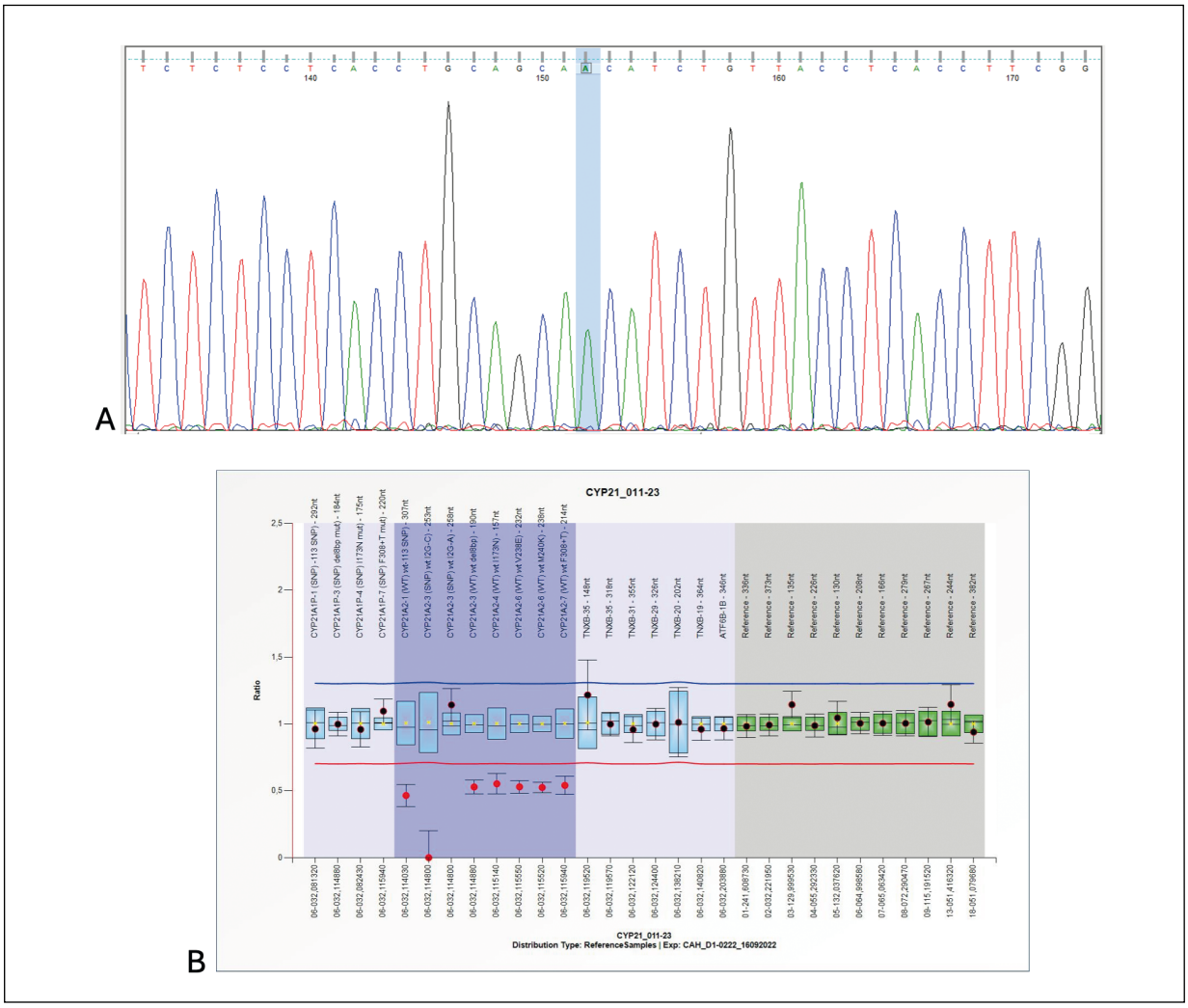

Figure 1. *A*, Sanger Sequencing showed the variant c.515T>A in exon 4 of the CYP21A2 gene in homozygous state in proband; *B*, MLPA analysis detected a heterozygous deletion of exons 1, 3, 4, 6, and 7 in CYP21A2 gene in proband. *Source*: Original.

To further characterize the proband's genotype, parental segregation analysis was performed. MLPA and gene sequencing of the parents revealed that the father carried the c.515T>A variant in a heterozygous state, while the mother harbored a large heterozygous deletion of exons 1, 3, 4, 6, and 7 in the *CYP21A2* gene (Figure 2A and 2B).

As a result, the proband's genotype was determined to be compound heterozygous for c.515T>A and large deletion (c.515T>A/del), consistent with the SV form of CAH.

DISCUSSION

Our patient presented with early puberty and significantly advanced bone age. Blood tests revealed elevated basal 17-OHP levels, which further increased after ACTH stimulation, a biochemical profile initially suggestive of the non-classic form of 21-OHD. Given the strong suspicion of CAH, additional biochemical and genetic investigations were conducted. DBS analysis demonstrated a marked accumulation of 17-OHP, and the steroid profile obtained via UPLC-MS/MS confirmed the diagnosis of 21-OHD, displaying a characteristic steroidogenic pattern of this congenital disorder. Genetic analysis identified a *CYP21A2* genotype (c.515T>A/del), consistent with the classic SV form of CAH. Sequencing analysis revealed that the proband was a compound heterozygote for a severe missense mutation (c.515T>A; p.Ile172Asn) inherited from the father and a large deletion (exons 1, 3, 4, 6 and 7) inherited from the mother. Initial-

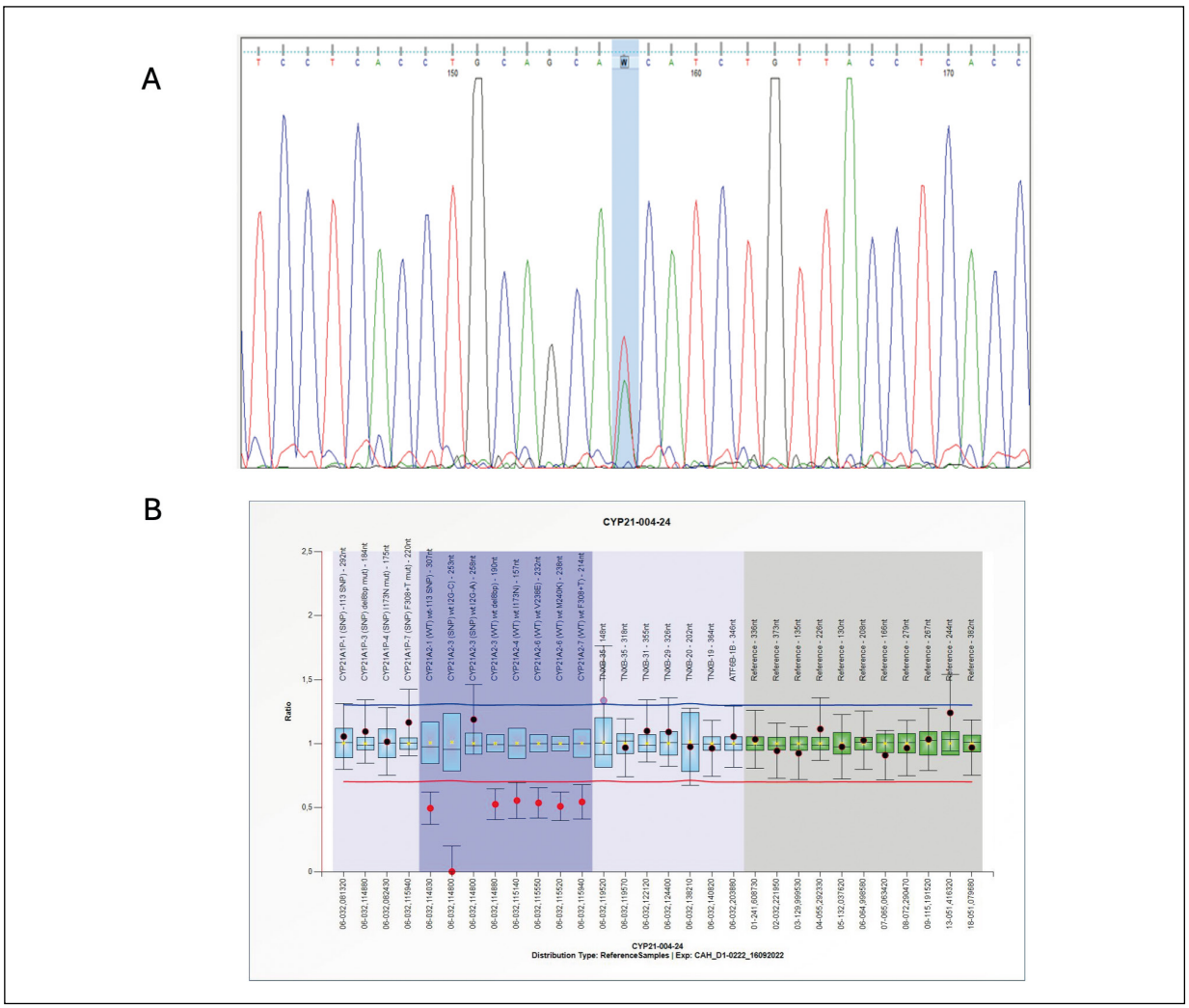

Figure 2. *A*, Sanger Sequencing identified the variant c.515T>A in exon 4 of the CYP21A2 gene in heterozygous state in proband's father; *B*, MLPA analysis detected a heterozygous deletion of exons 1, 3, 4, 6, and 7 in CYP21A2 gene in proband's mother. *Source*: Original.

ly, genetic analysis erroneously detected a homozygous c.515T>A genotype in the proband; however, parental segregation analysis clarified the correct heterozygous genotype. Indeed, due to the presence of heterozygous deletion, Sanger sequencing amplified only one allele, resulting in a false homozygous. The c.515T>A variant results in the substitution of isoleucine with asparagine at position 172 of the encoded protein (p.Ile172Asn). The large *CYP21A2* deletion (exons 1, 3, 4, 6, and 7) has been previously reported in the literature[10] but has not been documented in compound heterozygosity with the c.515T>A missense variant.

According to the EMQN best practice guidelines[11], this variant is classified as pathogenic and is responsible for the SV form of CAH, with approximately 1–2% residual 21-hydroxylase activity when present in homozygosity or compound heterozygosity. This finding contrasts with the initial clinical suspicion of non-classic CAH. Based on the confirmed diagnosis, the patient was started on hydrocortisone therapy (10 mg/m²/day) in three divided doses to centrally suppress adrenal androgen excess. The primary therapeutic goal was to stabilize bone age while ensuring normal growth. After 1 year of treatment, bone age advanced only slightly, and pubertal progression remained unchanged. This case underscores the importance of timely trio analysis and a multidisciplinary approach involving clinical, biochemical, and genetic evaluation for the accurate diagnosis of CAH and the implementation of targeted therapy.

Based on our review of the literature, the integration of biochemical and genetic analyses has been consistently demonstrated as essential for accurately identifying the specific form of CAH[12,13].

For example, Anastasovska et al[13] reported a case of a 14-day-old infant presenting with electrolyte imbalance and suspected SW CAH. Biochemical analysis revealed elevated 17-OHP, ACTH and testosterone levels. Genetic testing subsequently confirmed the diagnosis by identifying a genotype associated with the SW form. Similarly, Nasir et al[12] described a case of a 4-year-old boy born to consanguineous parents who initially presented with hyponatremia and hyperkalemia, raising suspicion of SW CAH. Further biochemical investigations showed increased 17-OHP and ACTH levels, while molecular testing identified compound heterozygosity consistent with the non-classic form, differing from the initial clinical suspicion. These cases underscore the critical role of combining biochemical and genetic analyses to accurately classify CAH subtypes and guide appropriate management. In this paper, we highlighted the importance of CAH screening for the early diagnosis of presymptomatic diseases. If the multidisciplinary approach is correctly applied, as described in the work, it could play a fundamental role. The synergistic combination of biochemical and genetic analysis allows for a timely diagnosis, favoring a rapid initiation of therapy. This process not only improves the patient's quality of life, but also reduces stress and anxiety for the family during the period of diagnostic uncertainty.

CONCLUSIONS

A multidisciplinary approach incorporating clinical, biochemical, and genetic analyses, supported by parental segregation, facilitates the early and accurate determination of CAH subtypes in cases of diagnostic uncertainty. This enables the implementation of appropriate therapies and helps prevent serious or potentially fatal complications associated with the classic form of CAH.

Therefore, our study contributes to expanding the existing literature and enhances the understanding of the biochemical and genetic aspects of congenital adrenal hyperplasia.

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No artificial intelligence-assisted technologies were used in the production of this article.

Authors' contributions:
Study conception and design: Marianna Ranaudo, Anastasia Dell'Elice; collection and interpretation of data: Marianna Ranaudo, Mirco Zucchelli, Maria Lucia Tommolini, Angelika Mohn; manuscript drafting: Marianna Ranaudo, Anastasia Dell'Elice, Aurora Navicella, Mirco Zucchelli, Maria Lucia Tommolini; manuscript editing: Aurora Navicella, Maria Minelli, Rossella Ferrante; approval to submit: Valentina Gatta.

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All data generated or analysed during this study are included in this published article or its supplementary material.

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The authors declare that they have no conflict of interest to disclose.

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ENSURING THE RIGHT TO ADEQUATE SCHOOL MENU FOR CHILDREN WITH METABOLIC OR KETOGENIC DIETS: A NATIONAL SURVEY OF CLINICAL AND FOOD SERVICE DIETITIANS

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***ABSTRACT* – Objective:** To examine approaches for managing school menus for special diets in Italy, highlighting regional variations and proposing strategies for improvement.

Materials and Methods: An online survey was developed by dietitians with expertise in ketogenic dietary therapies (KDTs) (*n=2*), inherited metabolic disorders (IMDs) (*n=5*), both KDTs and IMDs (*n=1*) and food services (*n=2*). The survey was distributed via e-mail to dietitians affiliated with the Technical Scientific Association of Food, Nutrition and Dietetics (ASAND) and with the Nutrition and Dietetics working group of the Italian Society for the Study of Inborn Errors of Metabolism and Newborn Screening (SIMMESN). The questionnaire included sections tailored to food service and clinical dietitians.

Results: A total of 165 dietitians participated, with 41% working in school food services and 21% specializing in IMDs or KDTs. Both clinical and food service dietitians reported challenges in managing IMD diets; ketogenic diets were perceived as significantly more complex, particularly by clinical dietitians. Major barriers included inadequate staff training in school food service, a lack of standardized protocols, and limited availability of specialized foods. Participants emphasized the importance of interdisciplinary collaboration, training programs, and standardized guidelines in improving school meal management.

Conclusions: Ensuring appropriate school nutrition for children with metabolic disorders is essential. Addressing existing gaps through policy development, professional training, and interdisciplinary collaboration is critical to optimizing dietary management and fostering inclusive school environments.

Keywords: Inherited metabolic diseases, Ketogenic dietary therapies, Special diets, Dietitians, Food service, School lunch menu.

List of abbreviations: ASAND: Technical Scientific Association of Food, Nutrition and Dietetics; IMDs: Inherited metabolic disorders; DRE: Drug-resistant epilepsy; GLUT1: Glucose-transporter type 1; KDTs: Ketogenic dietary therapies; SIMMESN: Italian Society for the Study of Inborn Errors of Metabolism and Newborn Screening.

INTRODUCTION

Inherited metabolic disorders (IMDs) comprise a diverse group of conditions affecting metabolic pathways responsible for the breakdown or storage of carbohydrates, fatty acids, and proteins[1,2]. These disorders can lead to multisystem complications. With the implementation of the Expanded Newborn Screening Program, many IMDs can now be detected within the first few days of life, enabling early intervention and reducing the risk of irreversible damage, often through the prompt initiation of dietary therapy[3]. Dietary management is fundamental to IMD treatment, as it involves restricting specific nutrients, ensuring scheduled meals to prevent fasting, and providing supplementation to avoid nutritional deficiencies. Depending on the affected metabolic pathway, dietary regimens may require the restriction of one or more macronutrient groups (e.g., proteins, fats, carbohydrates), precise gram-based portioning, the preparation of complex recipes, and the use of specialized medical foods[4].

Neurological and genetic conditions may also require strict dietary interventions to manage symptoms. Among these, drug-resistant epilepsy (DRE) and glucose-transporter type 1 (GLUT1) deficiency syndrome are notable for their treatment with ketogenic dietary therapies (KDTs)[5].

These specialized diets can be challenging for patients and caregivers, as they must be maintained long-term and require strict nutritional monitoring and regular follow-up to ensure proper dietary management. Therefore, dietitians play a crucial role in developing tailored nutritional interventions and promoting overall health based on the specific needs of each individual[6]. Children with metabolic disorders have distinct dietary requirements compared to adults, particularly due to their school and pre-school attendance. The school food environment constitutes a major part of their daily nutrition[7]. Integrating special diets into standard school food service systems is demanding for dietitians and school staff, who must exercise heightened vigilance and assume significant responsibility. The strict and precise requirements of dietary management of IMDs pose serious risks if not meticulously followed. Even minor deviations – such as accidental tray-switching among students or inadequacies in kitchen facilities – can have severe consequences[8].

According to guidelines from the Italian Ministry of Health[9], pre-school and primary school food services provide between one and five meals per week. School meals are designed to supply 35–40% of the average daily energy requirement. Consequently, school food services can serve as a communication channel with families, guiding appropriate choices for the evening meal – ensuring balanced daily and weekly dietary intake - and promoting an adequate, nutrient-rich breakfast. Modern school food services extend beyond ensuring food and nutritional safety, which are now considered fundamental prerequisites rather than primary objectives. They encompass broader functions, including disease prevention, health promotion, taste education, and fostering sociability, conviviality, and inclusion. These aspects contribute to a value that surpasses the mere provision of meals.

Despite these expanded roles, Italian school food service remains unregulated, and research on managing school lunches for pediatric patients with rare metabolic and neurological disorders is still limited. Addressing this gap could provide essential support to clinical professionals and food service staff in accommodating specialized dietary needs for which clear guidelines are currently lacking.

This study aims to examine approaches for managing school menus tailored to special diets, particularly those required for metabolic and neurological conditions, by focusing on clinical and food service dietitians at a national level. It seeks to identify regional variations in practice and provide insights for improving strategies.

MATERIALS AND METHODS

An online survey comprising 46 multiple-choice and short-answer questions (**Supplementary Material**) was developed by an expert panel consisting exclusively of dietitians with diverse expertise: two specialized in KDTs, five in IMDs, one in both KDTs and IMDs and two in food services. The survey was distributed via e-mail to dietitians affiliated with the Technical Scientific Association of Food, Nutrition and Dietetics (ASAND) – the national association representing dietitians across all areas of practice – and to the members of the Nutrition and Dietetics working group of the Italian Society for the study of Hereditary Metabolic Diseases and Newborn Screening (SIMMESN).

The questionnaire was developed in Italian and included an initial section with general questions (e.g., study title and years of experience in the field), followed by two specialized sections focusing on school food service management (A) and the dietary management of metabolic and neurological disorders (B).

A) School food service: the survey investigated how school food services manage special meal requests for pediatric patients with rare metabolic or neurological disorders. It examined key aspects such as menu planning, food preparation, monitoring dietary compliance, and challenges related to logistics, nutrition, and communication. Additionally, the survey explored potential improvements, including staff training programs and the implementation of standardized protocols for special diets.

B) Clinical dietitians working with IMDs or rare neurological diseases requiring KDTs:

the survey assessed the role of clinical dietitians in adapting school menus for pediatric patients on special diets and their collaboration with school food services to ensure adherence to strict dietary protocols and nutrient requirements. It also examined whether menu standardization could enhance the efficiency of dietary management in schools.

Participants were asked to complete the survey based on data collected from mid-November to mid-December 2024. Ethical approval was not required as no patients data were included.

Statistical analysis

Descriptive statistics were used to analyze the data, while responses from open-ended questions were categorized and presented by topic.

RESULTS

Characteristics of the Sample – General section

The survey received a total of 165 responses. Of these, 63 (38%) were excluded from the analysis because respondents reported having no experience in food service, IMDs or KDTs. Among the remaining responses, 68 (41%) were from food service dietitians; only 40 (24% of the total sample) had experience with metabolic or ketogenic diets. Thirty-four (21%) responses were obtained from clinical dietitians involved in dietary treatments for inherited metabolic disorders or ketogenic therapies. **Figure 1** illustrates the survey methodology, detailing the number of dietitians involved and the selection process for each group. The majority of survey participants (35%, 58/165) were aged 26–35 years, followed by 24% (39/165) aged 36–45 years. Participants aged 46–55 years and over 56 years accounted for 18% (29/165) and 17% (28/165), respectively, while those under 25 years comprised 6% (11/16) of the sample. Regarding professional experience as dietitians and in school food service, 33% (54/165) of respondents reported over 20 years of experience, followed by 26% (43/165) with 11-20 years of experience. Additionally, 22% (36/165) had 6–10 years of experience, while 19% (32/165) had worked in the field for less than 5 years. Regarding education, the majority of respondents (90%, 149/165) held a Bachelor's degree in dietetics, often with additional qualifications, such as a Master's degree or PhD. A smaller proportion had degrees in biology (9%, 15/165) or in food technology (1/165). **Table 1** presents demographic characteristics and professional experience in relation to educational

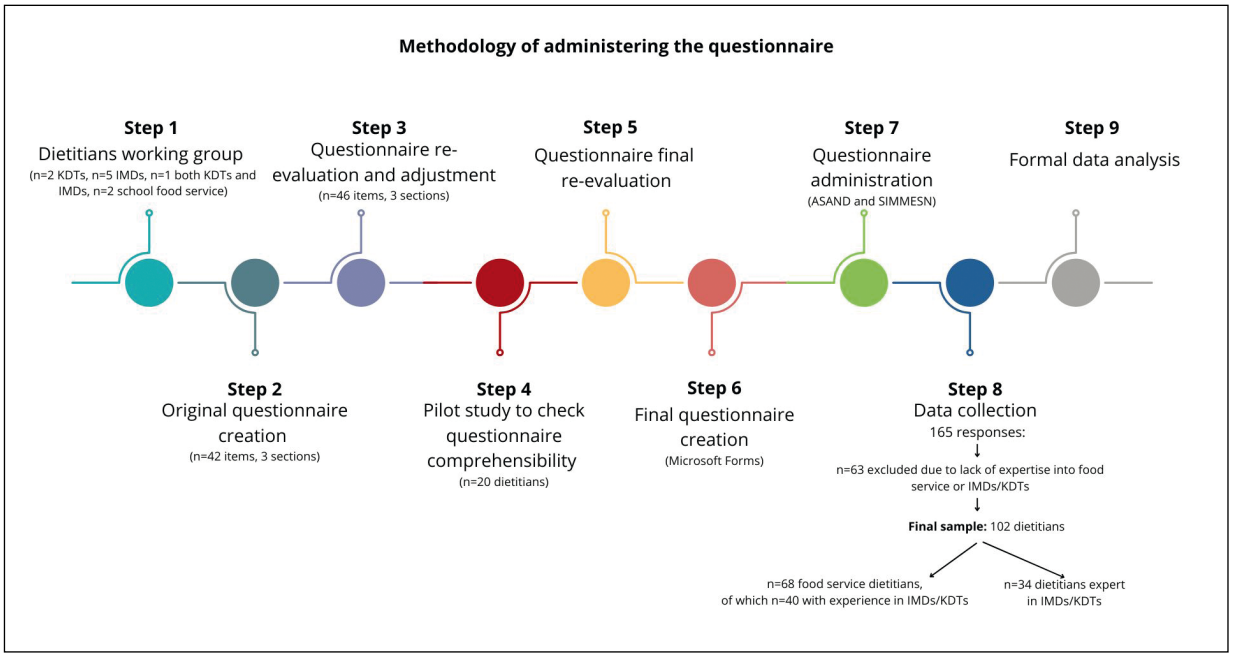

Figure 1. Illustration of the methodology for questionnaire administration, detailing the number of dietitians involved, the data collection process, and the criteria for response selection across participants.

background across different professional areas. Geographically, most participants were from Lombardia (18%, 29/165), Veneto (15%, 25/165), Toscana (10%, 17/165), and Emilia-Romagna (10%, 17/165). Other regions (Abruzzo, Calabria, Campania, Friuli Venezia Giulia, Lazio, Liguria, Marche, Molise, Piemonte, Puglia, Trentino Alto adige, Umbria) were less represented, whereas no responses were received from Valle d'Aosta, Sicilia, Sardegna and Basilicata.

Results among dietitians from School Food Service – Section A

Specific questions regarding school food service were included in Section A of the questionnaire. During their professional experience, 59% (40/68) of respondents reported having received requests for special meals for children with inherited metabolic or rare neurological disorders, while 41% (28/68) stated they had never received such requests. Among respondents who had managed special diet requests for children with rare neurological disorders undergoing ketogenic therapy or inherited metabolic disorders, 30/40 asked parents to plan the school menu, 20/40 trained food service staff, 22/40 forwarded the medical certificate to the special diet section of the central kitchen, and 15/40 consulted the child's clinical reference center. The most frequently reported challenge in managing special diets was inadequate training on diseases and therapies, followed by the high cost of the required foods, the need for training food service personnel and difficulties in gaining parents' trust. Regarding the time required to implement a special metabolic or ketogenic diet in schools: 42.5% (17/40) of the participants reported needing less than 3 days, 40% (16/40) required 3 days to 1 week, and 10% (4/40) took 1–2 weeks. Longer implementation times (over 2 weeks) were uncommon, reported by 7.5% (3/40) (**Figure 2A**). Regarding resources for managing special diets: 26/40 highlighted joint meetings involving dietitians, parents, and teachers, 18/40 proposed adaptable recipe books, 15/40 suggested menu standardization, and 15/40 considered infographics on rare disease diets helpful. When asked about adapting recipes to standard menus, 47.5% (19/40) reported rarely doing so, only for specific cases, 42.5% (17/40) stated they often adapted recipes, and 10% (4/40) reported never being able to adapt menus, citing time and organizational constraints. Finally, only 20% (8/40) indicated that explicit requests for specific products, such as food for special medical purposes, were included in food service contracts.

Table 1. General information of respondents.

General information	Results				
	Food service respondents with experience in metabolic or ketogenic diets (*n*=40), % (*n*)	Food service all respondents (*n*=68), % (*n*)	Dietitian involved in IMDs/ KDTs, (*n*=34), % (*n*)	Total respondents with experience in metabolic or ketogenic diets (*n*=74), % (*n*)	All respondents (*n*=165), % (*n*)
Age range					
<25 years	5.0 (2)	10.3 (7)	2.9 (1)	4 (3)	6.7 (11)
26–35 years	42.5 (17)	42.7 (29)	47.1 (16)	44.6 (33)	35.2 (58)
36–45 years	17.5 (7)	16.2 (11)	29.4 (10)	23.0 (17)	23.6 (39)
46–55 years	17.5 (7)	17.6 (12)	5.9 (2)	12.2 (9)	17.6 (29)
>55 years	17.5 (7)	13.2 (9)	14.7 (5)	16.2 (12)	16.9 (28)
Experience as a dietitian or another figure					
<5 years	20.0 (8)	29.4 (20)	11.8 (4)	16.2 (12)	19.4 (32)
6–10 years	27.5 (11)	22 (15)	35.3 (12)	31.1 (23)	21.8 (36)
11–20 years	22.5 (9)	20.6 (14)	29.4 (10)	25.7 (19)	26.1 (43)
>20 years	30.0 (12)	28 (19)	23.5 (8)	25.7 (20)	32.7 (54)
Degree					
Dietetic diploma	5.0 (2)	4.5 (3)	0.0 (0)	2.7 (2)	6 (10)
Dietetics Bachelor's degree	50.0 (20)	38.2 (26)	35.3 (12)	43.2 (32)	35.2 (58)
Dietetics Bachelor's degree + Master's/PhD	27.5 (11)	38.2 (26)	58.8 (20)	41.9 (31)	49.1 (81)
Biology degree	15.0 (6)	17.6 (12)	5.9 (2)	10.8 (8)	9.1 (15)
Food technology degree	2.5 (1)	1.5 (1)	0.0 (0)	1.4 (1)	0.6 (1)
Experience in the reference field					
<5 years	30 (12)	–	32.4 (11)	31.1 (23)	–
6–10 years	22.5 (9)	–	26.4 (9)	24.3 (18)	–
11–20 years	25 (10)	–	20.6 (7)	23 (17)	–
>20 years	22.5 (9)	–	20.6 (7)	21.6 (16)	–

Sixty-three answers (38%) were not analyzed because respondents were without experience in food service, IMDs or KDTs. *Abbreviations* - IMDs=inherited metabolic diseases. KDTs=ketogenic diet therapies.

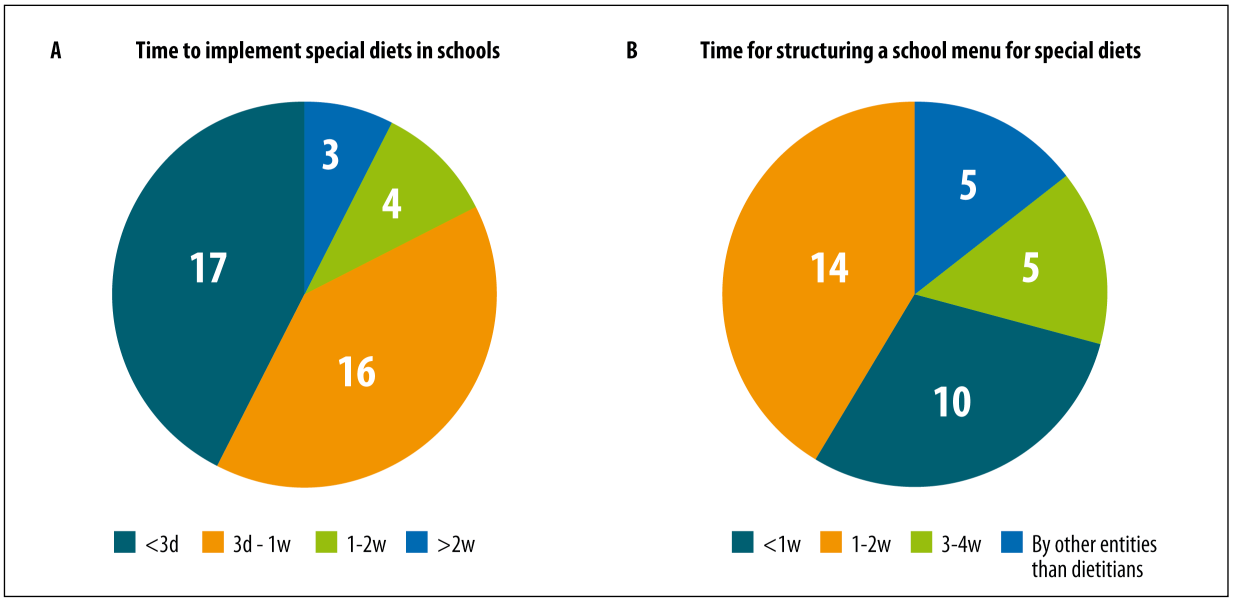

Figure 2. *A*, Time to implement special diets in school. *B*, Time for structuring a school menu for special diets.

Results from Dietitians Dedicated to Patients with Inherited Metabolic or Neurological Diseases – Section B

Section B of the questionnaire focused on clinical dietitians providing nutritional assistance to patients with inherited metabolic or neurological diseases. During their professional experience, 59% (20/34) of respondents primarily managed dietary therapy for inherited metabolic disorders, while 18% (6/34) specialized in ketogenic therapies for drug-resistant epilepsy or GLUT1 deficiency. The remaining 23% (8/34) worked in both areas. When structuring a school menu for a metabolic and/or ketogenic diet, 29% (10/34) required less than a week, 41% (14/34) needed 1–2 weeks, 15% (5/34) took 3–4 weeks, and 15% (5/34) indicated that menus were prepared by another professional (**Figure 2B**). Most clinical dietitians (88%, 30/34) reported being contacted by school food services for requests or clarifications. About 76% (26/34) of participants reported instances where families independently prepared school menus for their children. Among these, 19% (5/26) stated this occurred frequently, 58% (15/26) reported it happened occasionally, and 23% (6/26) indicated it occurred rarely. The remaining 23% (8/34) stated they had never encountered such cases (**Figure 3A**). Among respondents who reported that families were allowed to bring meals from home (79%, 27/34), 22.2% (6/27) indicated this happened frequently, 33.3% (9/27) occasionally, and 44.5% (12/27) rarely, while 21% (7/34) had never encountered such cases (**Figure 3B**). Regarding support for dietary management in schools, 30/34 recommended organizing informative meetings with food service dietitians, families, and school staff, 21/34 suggested specific training for dietitians in school food service, 19/34 emphasized the need for increased availability of medical-purpose foods. Additionally, 25/34 supported collaboration pathways between clinical centers, food services, and schools, 15/34 proposed specialized recipe books, and 15/34 recommended informative materials for parents and teachers. Most respondents (88%, 30/34) reported never actively training food service staff. A minority provided training either for groups (3/34) or individuals (1/34) on a regular basis. When asked who primarily develops special menus for metabolic or rare neurological diseases, dietitians at clinical centers were responsible for 65% (22/34) of cases, and dietitians from food service companies, after consulting clinical centers, in 26% (9/34) of cases. Other entities, such as public health institutions were involved in 9% (3/34) of cases.

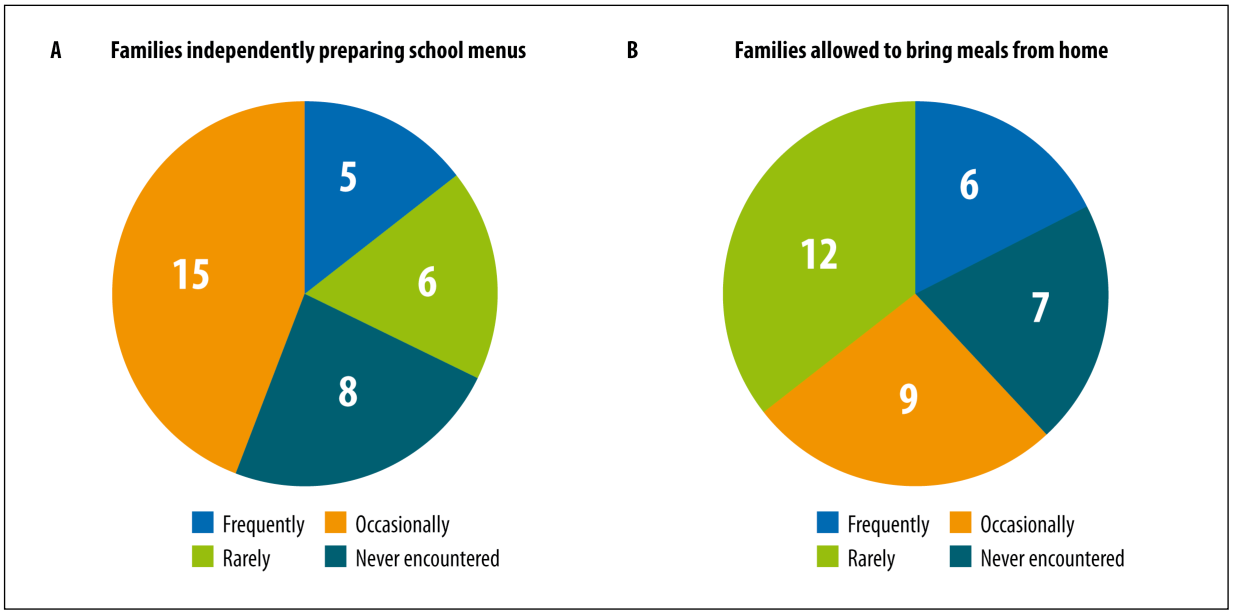

Figure 3. *A*, Families independently preparing school menus. *B*, Families allowed to bring meals from home. *Abbreviations* - d: days; w: weeks.

Questions targeting all professional figures – Section C

Respondents were asked to evaluate the level of difficulty in managing various special diets by the food service using a five-point scale: score 1: easy – 5: very difficult (see **Table 2** for detailed information). The diets receiving the highest difficulty scores (≥4) were ketogenic dietary therapies (62%), low-protein (35%) and sucrose, fructose, sorbitol-free diets -free diets (34%), low-fat diets (26%) and galactose-free diets (19%). All other dietary regimens received difficulty scores of 4 or 5 in fewer than 10% of cases. When comparing responses from food service dietitians and IMD/KDTs specialists, ketogenic dietary therapies, low-protein, low-fat, sucrose, fructose, sorbitol-free and galactose-free diets were consistently perceived as the most difficult to manage. Among participants involved in both school food service and special diet management, the diets that could potentially be standardized – at least partially – in the future included low-protein diets (29/74), low-fat diets (32/74), controlled carbohydrates diets (34/74), galactose-free diets (44/74), sucrose, fructose, sorbitol-free diets (32/74), and ketogenic diets (19/34). In contrast, other special diets - including gluten-free, egg-free, nut-free, tomato-free, fish-free, and diets for favism - were considered easier to manage compared to metabolic or ketogenic diets.

DISCUSSION

This study aimed to explore approaches for managing school menus for special diets, particularly those required for metabolic and neurological conditions. The findings highlight the complexity of accommodating school meals for children with IMDs or requiring KDTs and underscore unmet needs. Our results indicate that more than half of school food service dietitians have managed such diets, suggesting that they are not as rare as often assumed. Both clinical and food service dietitians reported similar challenges in managing IMD diets; however, KDTs were perceived as more difficult by clinical dietitians. This discrepancy likely arises from the complex calculations and individualized tailoring required for KDTs despite their relative ease of adaptation due to the availability of recipes requiring minimal modifications. In contrast, IMD diets are more adaptable to standard school menus, making them less challenging for both groups. Furthermore, metabolic or ketogenic special diets were considered more difficult to manage compared to dietary accommodations for common allergies and intolerances. Enhancing training and collaboration between healthcare professionals and school staff could improve the management of these specialized diets. Interdisciplinary collaborative meetings

Table 2. Evaluation of difficulties in managing various special diets by the food service.

Diet type	Difficulty	Results		
		Food service (*n*=40), % (*n*)	IMD and KDTs (*n*=34), % (*n*)	Total (*n*=74), % (*n*)
rs Low-protein	1 (easy)	14.7 (5)	17.6 (6)	16.2(12)
	2	23.5 (8)	14.7 (5)	17.6 (13)
	3	35.3 (12)	23.5 (8)	27.0 (20)
	4	23.5 (8)	26.5 (9)	23.0 (17)
	5 (very difficult)	11.8 (4)	14.7 (5)	12.2 (9)
	I don't know	5.9 (2)	2.9 (1)	4.1 (3)
Low-fat	1 (easy)	14.7 (5)	23.5 (8)	18.9 (14)
	2	20.6 (7)	23.5 (8)	20.3 (15)
	3	29.4 (10)	32.4 (11)	28.4 (21)
	4	23.5 (8)	11.8 (4)	16.2 (12)
	5 (very difficult)	14.7 (5)	5.9 (2)	9.5 (7)
	I don't know	11.8 (4)	2.9 (1)	6.8 (5)
Galactose-free	1 (easy)	26.5 (9)	17.6 (6)	21.6 (16)
	2	35.3 (12)	41.2 (14)	35.1 (26)
	3	17.6 (6)	20.6 (7)	17.6 (13)
	4	8.8 (3)	11.8 (4)	9.5 (7)
	5 (very difficult)	14.7 (5)	5.9 (2)	9.5 (7)
	I don't know	11.8 (4)	2.9 (1)	6.8 (5)
Fructose-free				
Sucrose, fructose, sorbitol-free diets	1 (easy)	17.6 (6)	11.8 (4)	13.5 (10)
	2	17.6 (6)	32.4 (11)	24.3 (18)
	3	17.6 (6)	23.5 (8)	18.9 (14)
	4	23.5 (8)	14.7 (5)	17.6 (13)
	5 (very difficult)	20.6 (7)	14.7 (5)	16.2 (12)
	I don't know	17.6 (6)	2.9 (1)	9.5 (7)

Continued

Table 2 *continued*. Evaluation of difficulties in managing various special diets by the food service.

Diet type	Difficulty	Results		
		Food service (*n*=40), % (*n*)	IMD and KDTs (*n*=34), % (*n*)	Total (*n*=74), % (*n*)
Ketogenic Dietary Therapy	1 (easy)	0.0 (0)	5.9 (2)	4.1 (3)
	2	14.7 (5)	2.9 (1)	8.1 (6)
	3	32.4 (11)	0.0 (0)	14.9 (11)
	4	8.8 (3)	17.6 (6)	12.2 (9)
	5 (very difficult)	35.3 (12)	73.5 (25)	50.0 (37)
	I don't know	23.5 (8)	0.0 (0)	10.8 (8)
Gluten-free	1 (easy)	73.5 (25)	55.9 (19)	60.8 (45)
	2	23.5 (8)	29.4 (10)	24.3 (18)
	3	5.9 (2)	11.8 (4)	8.1 (6)
	4	2.9 (1)	2.9 (1)	2.7 (2)
	5 (very difficult)	5.9 (2)	0.0 (0)	2.7 (2)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)
Eggs-free	1 (easy)	76.5 (26)	55.9 (19)	62.2 (46)
	2	26.5 (9)	29.4 (10)	25.7 (19)
	3	2.9 (1)	11.8 (4)	6.8 (5)
	4	2.9 (1)	2.9 (1)	2.7 (2)
	5 (very difficult)	2.9 (1)	0.0 (0)	1.4 (1)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)
Nuts-free	1 (easy)	67.6 (23)	44.1 (15)	52.7 (39)
	2	23.5 (8)	41.2 (14)	29.7 (22)
	3	8.8 (3)	11.8 (4)	9.5 (7)
	4	5.9 (2)	2.9 (1)	4.1 (3)
	5 (very difficult)	5.9 (2)	0.0 (0)	2.7 (2)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)
Favism	1 (easy)	70.6 (24)	67.6 (23)	64.9 (48)
	2	23.5 (8)	20.6 (7)	20.3 (15)
	3	5.9 (2)	5.9 (2)	5.4 (4)
	4	5.9 (2)	2.9 (1)	4.1 (3)
	5 (very difficult)	5.9 (2)	0.0 (0)	2.7 (2)
	I don't know	2.9 (1)	2.9 (1)	2.7 (2)

Continued

Table 2 *continued*. Evaluation of difficulties in managing various special diets by the food service.

Diet type	Difficulty	Results		
		Food service (*n*=40), % (*n*)	IMD and KDTs (*n*=34), % (*n*)	Total (*n*=74), % (*n*)
Tomato-free	1 (easy)	79.4 (27)	67.6 (23)	68.9 (51)
	2	17.6 (6)	23.5 (8)	18.9 (14)
	3	5.9 (2)	8.8 (3)	6.8 (5)
	4	5.9 (2)	0.0 (0)	2.7 (2)
	5 (very difficult)	2.9 (1)	0.0 (0)	1.4 (1)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)
Fish-free	1 (easy)	88.2 (30)	67.6 (23)	73.0 (54)
	2	8.8 (3)	23.5 (8)	14.9 (11)
	3	8.8 (3)	2.9 (1)	5.4 (4)
	4	0.0 (0)	5.9 (2)	2.7 (2)
	5 (very difficult)	5.9 (2)	0.0 (0)	2.7 (2)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)
Low-sodium	1 (easy)	44.1 (15)	88.2 (30)	62.2 (46)
	2	35.3 (12)	11.8 (4)	21.6 (16)
	3	14.7 (5)	0.0 (0)	6.8 (5)
	4	11.8 (4)	0.0 (0)	5.4 (4)
	5 (very difficult)	2.9 (1)	0.0 (0)	1.4 (1)
	I don't know	5.9 (2)	0.0 (0)	2.7 (2)
Diet for diabetes	1 (easy)	35.3 (12)	50.0 (17)	40.5 (30)
	2	35.3 (12)	35.3 (12)	32.4 (24)
	3	23.5 (8)	11.8 (4)	16.2 (12)
	4	11.8 (4)	2.9 (1)	6.8 (5)
	5 (very difficult)	2.9 (1)	0.0 (0)	1.4 (1)
	I don't know	5.9 (2)	0.0 (0)	2.7 (2)
Diet for dysphagia	1 (easy)	26.5 (9)	17.6 (6)	21.6 (16)
	2	32.4 (11)	52.9 (18)	39.2 (29)
	3	41.2 (14)	14.7 (5)	25.7 (19)
	4	2.9 (1)	11.8 (4)	6.8 (5)
	5 (very difficult)	8.8 (3)	2.9 (1)	5.4 (4)
	I don't know	2.9 (1)	0.0 (0)	1.4 (1)

Abbreviations - IMD=inherited metabolic diseases; KDTs=ketogenic dietary therapies.

represent a promising strategy to to strengthen communication, equip professionals with the necessary skills, and ensure more effective dietary management. This approach could ultimately enhance health outcomes and daily quality of life for children and their families. **Figure 4** illustrates the complex collaboration between clinical dietitians specialized in IMDs or/and KDTs and school food services, detailing the school meal request process, challenges encountered, and potential solutions. School meals play a crucial role in children's daily nutrition, providing up to 35-40% of their total daily intake, according to the Italian Healthy Eating Guidelines 2018[10].

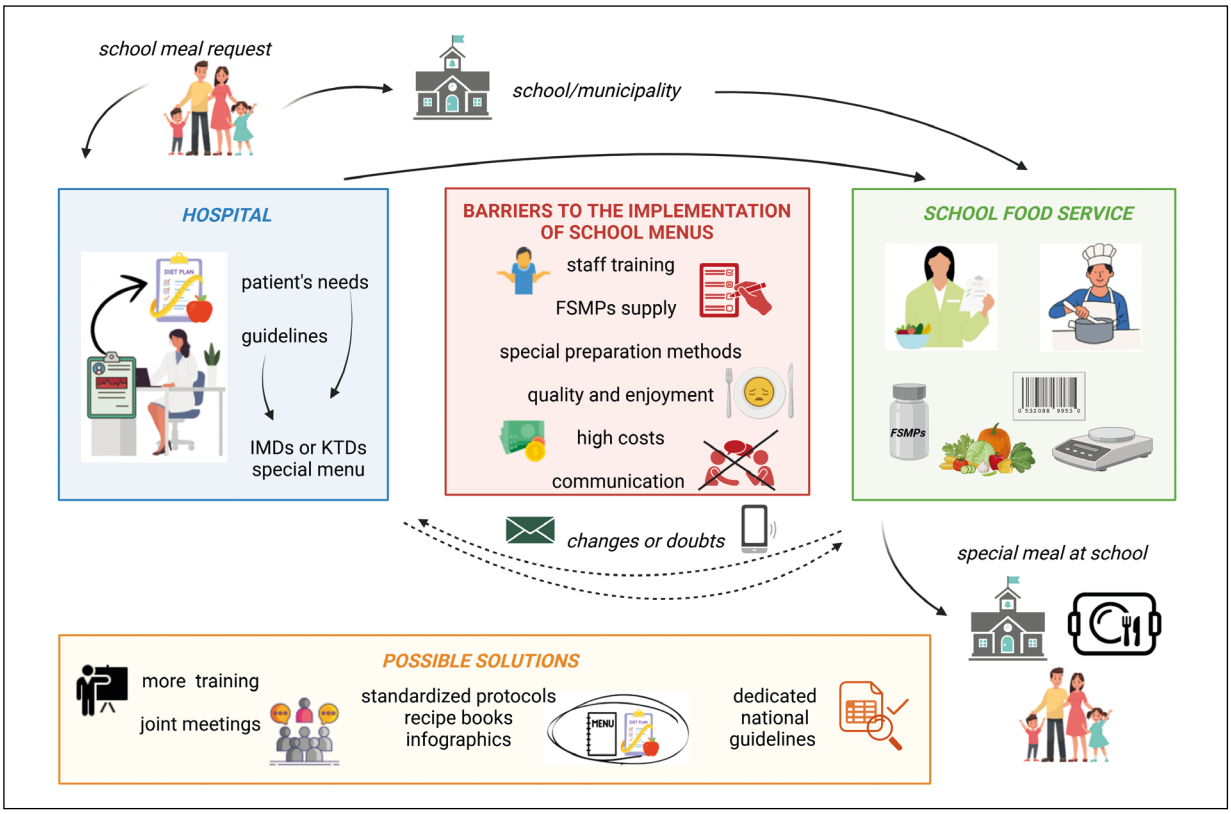

Figure 4. Collaboration between clinical dietitians specialized in IMDs and/or KTDs and school food services. It also includes the main challenges identified and possible solutions proposed.

For children with special dietary needs, particularly those with IMDs or DRE and GLUT1 deficiency syndrome, properly tailored meals are even more critical, as their diet functions as a therapeutic intervention. It is, therefore, essential that school food services are designed to meet the specific dietary requirements. However, while legal provisions exist for children with celiac disease (Law 123/2005), no specific legislation currently addresses school meal accommodations for children with IMDs or DRE or GLUT1 deficiency syndrome. The National Guidelines for Hospital/Care and School Foodservice (2021)[9] recognize food service as a key component of public health, emphasizing its role in the prevention and treatment of nutrition-related diseases in both healthcare and school settings. The guidelines recommend that school food services provide tailored meals for children with clinical conditions (allergies/intolerances), as well as for cultural, ethical, or religious dietary needs. Despite these recommendations, a regulatory gap remains in ensuring comprehensive protections for children with IMDs or DRE and GLUT1 deficiency syndrome, underscoring the need for stronger policies to guarantee appropriate nutritional support in schools. Current national guidelines for managing special diets in school food service require a medical certificate from the child's primary care pediatrician or specialist. While special diets for celiac disease or food allergies are well-documented through established guidelines and operational procedures, making them easier to standardize, IMDs and KDTs present additional challenges that require individualized planning and greater policy attention. Furthermore, there is often no clear designation of responsibility for managing the implementation of special diets in schools. International frameworks, such as the Vienna Declaration on the Right to Nutritional Care[11], emphasize that nutritional care is a fundamental human right closely linked to the

right to food and health. For children following metabolic or ketogenic diets, ensuring that their dietary needs are met at school is crucial for disease management and healthy growth. However, the level of support for children with special dietary needs in schools varies significantly between countries. In the USA, the legislation mandates that school food services provide special meals at no additional cost to children whose disability restrict their diet, in accordance with USDA's[12] non-discrimination regulations. This policy ensures that children with medical conditions are not excluded from proper nutrition during school hours. In the UK, the Children and Families Act (2014) requires schools to support children with medical conditions, including those with inherited metabolic disorders such as phenylketonuria (PKU)[13]. Schools must collaborate with healthcare professionals, parents, and children to meet their dietary needs, while also implementing staff training programs and policy development to ensure proper accommodation of dietary requirements. Since all children are entitled to a school meal, food services are expected to work with parents and medical professionals to provide safe, inclusive meal options for children with PKU, as outlined in a national PKU patients' association guide[14]. By contrast, in Italy, while standardized procedures exist for common dietary accommodations (e.g., celiac disease, food allergies), guidelines for personalized diets (e.g., metabolic disorders, ketogenic diet therapy) remain insufficient. There is no national policy defining who is responsible for approving and overseeing these specialized menus, and prescriptions from specialized centers vary by region, often lacking clarity and consistency. Beyond the need for legislation and food service guidelines, it is also important to recognize that implementing these specialized dietary approaches imposes a significant workload on food service providers, healthcare professionals, and families. This burden associated with managing specialized diets, as reported by the dietitians in this survey, should be carefully considered from an organizational perspective to ensure adequate allocation of resources for dietitians working in both food service and clinical nutrition services.

Limitations

One limitation of this study is the potential for selection bias, as the survey was distributed voluntarily by invitation. This may have led to anoverrepresentation of dietitians from northern Italy, limiting the sample's representativeness of the entire population of Italian dietitians. Moreover, the survey did not assess the perceptions and barriers experienced by patients and families regarding access to school meals, which is an important aspect of the right to food.

On the other hand, this study is the first of its kind to evaluate and compare the activities of dietitians working in food service and clinical nutrition for IMDs and KDTs on a national scale. Efforts were made to maximize participation through the dual-channel distribution via ASAND and the Nutrition and Dietetic working group of SIMMESN. By identifying shared challenges and unique difficulties within each field, this study underscores the need for greater collaboration and networking among professionals to enhance the management of special diets in schools.

CONCLUSIONS

Providing appropriate meals for children with metabolic disorders is not only a nutritional requirement but also a fundamental human right. This study highlights the challenges of integrating special diets into school food services, particularly the complexity of ketogenic diets. To create a more inclusive school environment and optimize school meal provisions for children with rare metabolic and neurological disorders, an interdisciplinary collaboration between healthcare professionals and school staff, professional education for dietitians and food service personnel, standardized protocols for managing special diets, and policy alignment with international standards to ensure equal access to adequate nutrition are essential. By implementing these measures, schools can better support children with IMDs and rare neurological conditions, ensuring that their right to proper nutrition is upheld.

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THE ROLE OF PATERNAL ENGAGEMENT IN PHENYLKETONURIA: EXPLORING PSYCHOLOGICAL OUTCOMES IN CHILDREN

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ABSTRACT **– Objective:** This study investigates the psychological outcomes of children with phenylketonuria (PKU) and their fathers, focusing on the impact of paternal engagement on child psychological well-being, quality of life, and metabolic control.

Patients And Methods: A monocentric prospective observational study was conducted on a cohort of 30 fathers and their children with PKU (aged 6–12 years) at the University Hospital of Padua (Italy). Psychological assessments included the Phenylketonuria – Quality of Life questionnaire (PKU-QOL), the Intolerance of Uncertainty Scale for children, and the Parenting Stress Index Short Form (PSI-SF), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7) for fathers. An *ad hoc* questionnaire was developed to measure paternal engagement in disease management. Correlation and regression analyses were performed to explore associations between paternal involvement, psychological functioning, and metabolic control.

Results: Fathers reported a generally high level of engagement, though some expressed feelings of guilt over the genetic transmission of PKU and perceived their role as secondary to mothers. Higher paternal engagement was associated with lower parental stress, improved child quality of life, and reduced intolerance of uncertainty. Regression analysis revealed that paternal stress and engagement significantly predicted children's quality of life, highlighting the relevance of psychological and family dynamics in disease management.

Conclusions: Encouraging paternal involvement in PKU care positively impacts both children and fathers, contributing to better psychological well-being and adherence to treatment. Healthcare professionals should recognize and support the role of fathers to optimize family-centered care in PKU management.

Keywords: Paternal engagement, PKU, Engagement, Parenting stress, Quality of life.

List of abbreviations: GAD-7: Generalized Anxiety Disorder-7; Phe: phenylalanine; PKU: Phenylketonuria; PKU-QOL: Phenylketonuria – Quality of Life; PSI-SF: Parenting Stress Index Short Form; Tyr: tyrosine.

INTRODUCTION

Phenylketonuria (PKU) is a rare inherited metabolic disorder that is caused by a deficiency in the enzyme phenylalanine hydroxylase, which is responsible for converting the amino acid phenylalanine (Phe) into tyrosine (Tyr). The absence of timely treatment leads to a neurotoxic accumulation of Phe, leading to neurological damage, including intellectual disability and epilepsy[1,2].

PKU is the most common amino acid metabolism disorder, with a global prevalence of approximately 1:23,930 live births[3]. The prevalence varies significantly worldwide, ranging from 1:4,500 in Italy to 1:100,000 in populations, such as Finnish, African and Japanese[4].

Thanks to newborn screening, nowadays, it is possible to achieve an early diagnosis and initiate treatment promptly in the first days of life, thus preventing severe brain damage[1]. There are several forms of hyperphenylalaninemia, from the most severe classical PKU (Phe levels at birth >1200 µmol/l) to the moderate form (Phe levels at birth 600–1200 µmol/l), and finally, a mild form called mild hyperphenylalaninemia (Phe levels at birth 360–600 µmol/l), which typically does not require treatment[5,6].

The mainstay treatment for PKU is generally dietary therapy, which includes controlling protein intake combined with supplementation of amino acid mixtures and vitamins[3]. However, other therapies are now available: sapropterin dihydrochloride, a synthetic form of the cofactor tetrahydrobiopterin, and pegvaliase, a recombinant phenylalanine ammonia lyase enzyme that catalyzes the conversion of Phe through an alternative enzymatic pathway. These therapies aim to allow for better control of Phe levels and greater dietary flexibility, sometimes leading to a completely unrestricted diet[7]; however, these treatments are not suitable for all patients. The management of dietary therapy is reported to have a significant impact on the daily lives of patients and their families, with difficulties arising in social situations due to the need to consume special foods or supplements for taste issues[8]. These difficulties can lead to challenges in adhering to the prescribed treatment[9].

The disease and its management may impact the well-being of patients, putting them at risk for experiencing stress, social anxiety, and depressive symptoms[10,11]. However, literature on the quality of life in PKU patients has yielded conflicting results, with some studies showing levels comparable to the general population[12].

Some studies have suggested that the diagnosis of a chronic illness, such as PKU, during childhood not only affects the well-being of the child but also impacts the entire family system[13]. Parents play a critical role in managing the disease: they are responsible for therapy, monitoring Phe levels, and planning medical visits[14]. Furthermore, some studies suggest that the daily life of parents is significantly affected by the considerable burden of the child's disease and its treatment[15]. Specifically, the most disruptive factor contributing to parental stress, as well as the patient's quality of life, is dietary restriction[16]. Adequate family involvement is essential for the well-being of children; indeed, a significant correlation between family engagement and the physical and psychological well-being of children with PKU was found[11].

However, most studies on the impact of chronic diseases on parents have focused only on mothers, who are typically the primary caregivers and at greater risk for caregiver burden[17,18]. However, the few studies on fathers highlighted that their exclusion from disease management may negatively affect both the well-being of mothers and the paternal identity, making fathers feel less effective in caring for their child and leading to frustration and a sense of helplessness regarding the disease[19].

Fathers strongly contribute to infant development and, in the last years, are spending more time with their children than in many past decades; therefore, assessing and supporting their involvement in family dynamics, particularly in illness conditions, is of primary importance[20]. In order to deeply explore the role of fathers in chronic diseases, in recent years, research has started to explore the concept of paternal engagement, which refers to the level of involvement, active participation, and commitment to managing the child's illness. Some studies have highlighted that greater paternal involvement in managing a chronic illness provides emotional and practical support, which can alleviate maternal anxiety and stress related to therapy management[21]. Furthermore, paternal engagement is associated with better psychological and behavioral outcomes in children[22,23]. One study demonstrated that young individuals with chronic conditions from families with absent fathers showed poorer treatment adherence and lower psychological adaptation and health outcomes[24]. Another study emphasized that treatment adherence decreases with lower paternal involvement[19].

Despite these findings, studies on the role of fathers in chronic diseases remain limited, particularly within PKU populations. For instance, a review by Taylor et al[25], which assessed father involvement in pediatric chronic illnesses, highlighted the need for increased research on this topic across various chronic conditions, emphasizing that paternal engagement is one of the most important challenges for future research in pediatric chronic conditions. Therefore, assessing and supporting paternal involvement in the management of PKU, which requires substantial parental oversight of therapy and biochemical values, is crucial. Therefore, this study aims to investigate the level of paternal involvement in children with PKU, focusing on its associations with the mental well-being of both fathers and children.

PATIENTS AND METHODS

Study design

This is a monocentric prospective observational study. Pediatric patients with PKU in care at the Unit of Metabolic and Hereditary Diseases at the University Hospital of Padua (Italy) and their fathers were invited to participate in the study. The inclusion criteria for patients were a PKU diagnosis confirmed through newborn screening and the patient's age between 6 and 12 years. Exclusion criteria were severe intellectual impairments preventing children from completing questionnaires, language comprehension difficulties, and having changed center of care in the previous year.

METHODS

Sociodemographic information

Sociodemographic and medical information regarding the fathers and children was collected through an *ad hoc* questionnaire specifically designed for this study, completed by the fathers. The following information was requested: the child's age and gender and the father's age, ethnicity, occupation, educational level, and marital status. Moreover, the presence of siblings with PKU and the presence of other diseases were requested.

Phe and Tyr levels

The Phe and Tyr levels of the children were obtained from their medical records. These values were measured in two different ways: analysis of blood spots sent from home by the parents or plasma levels of Phe and Tyr collected through blood draws during outpatient visits. Data from the past year were considered, and an annual mean of each patient's values was calculated.

CHILDREN

Phenylketonuria – Quality of Life

The questionnaire Phenylketonuria – Quality of Life (PKU-QOL)[26] was used to assess the children's quality of life related to their illness. This instrument was designed to evaluate the quality of life related specifically to PKU, assessing four variables of the condition: PKU symptoms, the general impact of PKU (physical, emotional, and social impact), administration of Phe-free protein supplements, and daily dietary restriction.

The PKU-QOL is available in four versions, one for each specific group: Children (age 9–11 years, 40 items), Adolescents (age 12–17 years, 58 items), Adults (65 items), and Parents (assessment of their children's and their own quality of life, 54 items). The questionnaire was primarily created in seven languages: English, French, German, Italian, Dutch, Spanish, and Turkish.

Patients or their caregivers are asked to give their agreement with the sentences on a Likert scale from 0 to 4, where higher scores indicate a greater negative impact on quality of life. A total score and one score for each module can be calculated, ranging from 0 to 100. Scores below 25 indicate little impact of PKU on patients' quality of life; scores between 25 and 50 reflect a moderate impact; scores between 50 and 75 indicate a major impact; and scores above 75 denote a severe impact[12].

Intolerance of Uncertainty Scale-12

The questionnaire Intolerance of Uncertainty Scale-12 was used to assess children's intolerance of uncertainty and the difficulty of a person in tolerating uncertain or ambiguous situations. This scale studies two main components: prospective intolerance of uncertainty and inhibitory intolerance of uncertainty. The first component relates to the need to seek information about an uncertain situation perceived as

threatening and intolerable; the second component involves an avoidance strategy that "freezes" the individual, leading to an inability to act and a tendency to procrastinate decisions[27].

The short version of the scale consists of 12 items, with responses provided on a 5-point Likert scale (from 1 = "strongly disagree" to 5 = "strongly agree"). The first seven items measure the level of prospective intolerance of uncertainty, while the last five items assess the degree of inhibitory intolerance. The sum score of the Intolerance of Uncertainty Scale (ranging from 27 to 135) and each scale's score was used in this study. Higher scores indicate higher intolerance of uncertainty.

The Italian version of the scale has been used with a youth sample in a previous study[28].

FATHERS

Engagement

An *ad hoc* questionnaire, formed of five open-ended questions, was developed to assess paternal involvement. Fathers were asked to answer each question with a short answer and subsequently to score their level of agreement with each statement on a Likert scale from 1 to 10, with lower scores indicating less agreement and higher scores indicating greater agreement. The total score is provided by summing the score of each question.

These questions were specifically designed for this study in collaboration with expert clinicians to examine in detail key aspects of fathers' engagement in managing their child's PKU. The instrument aimed to investigate five factors: control, being a reference figure, management of daily life, level of information, and perception of responsibility.

The questions included were:

- *Do you feel you have control over what happens in your child's life regarding the illness?*
- *Do you feel you are a reference figure for your child in relation to the illness?*
- *Do you feel that you actively contribute to managing your child's illness?*
- *Do you feel adequately informed about the illness?*
- *Do you feel in some way responsible for your child's illness?*

Parenting Stress Index Short Form

The Parenting Stress Index Short Form (PSI-SF)[29] was used to assess the parenting stress of the fathers. The PSI-SF is a self-report questionnaire consisting of 36 items designed to measure the level of stress in the parent-child relationship.

The PSI-SF is divided into three subscales: "Parental Stress", which evaluates the degree of discomfort that parents may feel in fulfilling their parenting role and the manner they approach their parenting responsibilities; "Dysfunctional Parent-Child Interaction", which is based on the expectations parents have of their child and the resulting lack of gratification within the relationship; and "Difficult Child", which is based on the child's temperament or behavioral characteristics that may cause difficulties and tension in managing the child, with higher scores in this subscale may indicate behavioral issues in the child. In addition to these subscales, the questionnaire includes control items that assess the parent's desire to present an idealized image of themselves and their relationship with the child, forming the Defensive Response scale.

The PSI-SF uses a 5-point Likert scale, with the total score obtained by summing the scores across all subscales. A higher total score indicates greater parental stress, more dysfunctional interactions, and greater difficulty in managing the child. As a clinical distress cut-off, we used the 85th percentile based on research norms[30].

Patient Health Questionnaire-9

The Patient Health Questionnaire-9, a nine-item self-report scale, was used to assess depressive symptoms in fathers[31]. The items assess potential depressive manifestations, such as difficulty falling asleep, lack of general interest, fatigue, low mood, reduced appetite, low self-esteem, slowed movements, and thoughts of death. After the nine items, there is a tenth item, which is excluded from the total score,

that specifically determines the level of impairment that depressive symptoms may cause in daily activities. Each item is scored on a Likert scale ranging from 0 to 3. Higher scores are related to higher levels of depressive symptoms; the scores are categorized as follows: 0–4 indicates the absence of symptoms, 5–9 represents subthreshold depression, 10–14 corresponds to mild major depression, 15–19 indicates moderate major depression and a score of 20 or higher denotes severe major depression. These categories help to assess the severity of depressive symptoms and may guide treatment decisions.

Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 (GAD-7), a brief self-report questionnaire, was used to assess anxiety symptoms in fathers[32]. It is composed of seven items, rated on a Likert scale from 0 to 3, and it was designed to identify generalized anxiety disorder and other related conditions. It is one of the few measures specifically aligned with DSM criteria. Higher scores indicate a greater presence of anxiety symptoms (cut off ≥15).

Study procedures

Participants were involved in the study both in person, during outpatient visits, and via e-mail. Families were subsequently re-contacted by e-mail for study participation if they had not responded to the initial e-mail. Consent for the participation of children with PKU was provided in writing by both parents, while fathers individually gave their consent to take part in the study.

Participants completed the questionnaires either on paper or through the online link provided to them.

All participants gave written informed consent before participation. The study was approved by the Local Ethics Committee (Ethics Committee Approval No. 6178AO25, University Hospital of Padua, Italy).

The principles of good clinical practice were adhered to throughout the study in accordance with the Declaration of Helsinki (as amended) and the International Conference on Harmonization/good clinical practice guidelines.

Statistical analysis

In the first section, the mean scores of the PKU-QOL and the Intolerance of Uncertainty Scale for children, as well as the PSI-SF, GAD-7, and Patient Health Questionnaire-9 scores for fathers, were calculated and presented in a table to assess the psychological well-being of the PKU population.

In the second section, paternal engagement scores are reported to highlight the quantitative outcomes of the questionnaire. Additionally, a qualitative analysis of fathers' responses to each open-ended question is provided.

In the third section, correlations between paternal engagement scores (both total scores and individual item scores) and the total scores of the patient and father questionnaires were assessed using Pearson's r correlation coefficient.

In the final section, a correlation model was developed to investigate factors that may predict children's quality of life. Potential predictors were identified by estimating correlation coefficients between the medical dimensions and psychological aspects of fathers and the total PKU-QOL score for patients.

RESULTS

Study Cohort

A total of 48 eligible children with PKU and their fathers were identified, and responses were received from 30 families (response rate = 62.5%). Ultimately, 28 children aged 6–12 years (mean = 9.7, SD = 2.1) were enrolled in the study, while the sample of fathers consisted of 30 participants aged between 32 and 72 years (mean = 45.5, SD = 7.8). Two children were excluded from the study due to lack of parental consent.

Within the patient sample, 17 were male (57%) and 13 were female (43%). The mean blood Phe level over the past year was 259.61 µmol/L (SD = 80.38), and the mean Tyr level was 74.80 µmol/L (SD = 18.62). 86% of the sample achieved adequate mean Phe levels, according to the European guidelines for children under 12 years[3], over the past year, while 14% exceeded this range. Of the children, 43% followed dietary therapy, while 57% did not require dietary treatment.

The sample of fathers was predominantly Caucasian (86.7%). Most fathers had completed high school education (56.7%), with the most common occupation being manual labor (23.3%), followed by administrative work (16.6%) and business ownership (13.3%). Most fathers (87%) reported being married, while 10% were cohabiting, and 3% were divorced. The majority of families had two or more children (86.7%), and in 13.3% of cases, there was another sibling with PKU.

Mean values of children's quality of life and intolerance of uncertainty

The mean scores of the psychological variables in children are reported in Table 1, generally within the normal range, with some exceptions. The average level of total quality of life indicates a perception of moderate impact. Specifically, on the scales "symptoms" and "daily dietary restrictions", the impact on quality of life is little, while on the scales "general impact" and "protein supplements" the average value indicates a moderate impact on quality of life. Total intolerance of uncertainty, as well as the "prospective" and "inhibitory" scales, fall within the normal range.

Table 1. Mean levels of children's quality of life and intolerance of uncertainty.

Psychological dimension	Scale	Mean	Standard deviation
Quality of life	PKU-QOL "symptoms"	22.94	15.56
	PKU-QOL "general impact"	30.09	10.15
	PKU-QOL "protein supplements"	28.68	16.05
	PKU-QOL "daily dietary restrictions"	11.61	22.02
	PKU-QOL "total"	26.26	11.60
Intolerance of uncertainty	IUS "prospective"	19.28	6.61
	IUS "inhibitory"	10.92	5.20
	IUS "total"	30.21	10.75

Mean values of fathers' parenting stress, anxiety symptoms, and depressive symptoms

The psychological variables of fathers showed mean scores within the normal range (Table 2).

Table 2. Mean levels of fathers' parental stress, anxiety and depression symptoms.

Psychological dimension	Scale	Mean	Standard deviation
Parental stress	PSI "difficult child"	22.63	7.62
	PSI "parent-child dysfunctional interaction"	19.33	7.09
	PSI "parental distress"	20.43	8.32
	PSI "total"	62.40	20.65
Anxiety	GAD-7 "total"	4.66	4.86
Depression	PHQ-9 "total"	3.70	3.67

Total parental stress, as well as the "difficult child," "parent–child dysfunctional interaction," and "parental distress" scales, show results fully within the normal range. The scores on the Defensive Response scale were within normal limits for all participants.

Similarly, the total mean scores on the anxiety and depression symptom scales fall within the normal range.

Paternal engagement

The data emerging from the quantitative responses are generally adequate in the total score and in almost all domains. Overall, a good level of perceived engagement is observed in the engagement domains "control", "reference figure", "disease management" and "information", while lower involvement is perceived by fathers in engagement responsibilities.

The mean score (score range 0–10) for each domain, total paternal engagement scores, and the number of responses in the low (scores 0–5) or high (scores 6–10) range of response are reported in Table 3.

Table 3. Mean levels and range of response of paternal engagement.

Scale	Mean (SD)	Range of response
Engagement "control"	7.37 (2.76)	0–5: *n*=7/30 (23.3%) 6–10: *n*=23/30 (76.7%)
Engagement "reference figure"	7.77 (2.38)	0–5: *n*=5/30 (16.7%) 6–10: *n*=25/30 (83.3%)
Engagement "disease management"	7.53 (2.40)	0–5: *n*=7/30 (23.3%) 6–10: *n*=23/30 (76.7%)
Engagement "information"	7.70 (2.00)	0–5: *n*=5/30 (16.7%) 6–10: *n*=25/30 (83.3%)
Engagement "responsibility"	4.37 (3.51)	0–5: *n*=20/30 (66.7%) 6–10: *n*=10/30 (33.3%)
Engagement "total"	34,73 (8,59)	0–25: *n*=5/30 (16.7%) 26–30: *n*=25/30 (83.3%)

The results of a more in-depth analysis of each question addressed to fathers regarding their perceived engagement in child management is presented below.

Do you feel you have control over what happens in your child's life regarding the illness?

The responses highlight that the majority of fathers (83.3%) report feeling they have adequate control over the disease, despite some emphasizing the effort required from parents to enable their child to lead a "normal life". However, some fathers (16.7%) report not feeling they have full or partial control over their child's PKU; in particular, concerns arise regarding the management of administrative issues related to the disease and the presence of other medical conditions in the child. Additionally, one parent explained relying on the sense of responsibility of their preadolescent daughter due to difficulties in managing the disease.

Do you feel you are a reference figure for your child in relation to the illness?

A generally positive perception emerged among the majority of fathers (73.3%), who perceive themselves as a primary reference figure for their child, often reporting that they share this role with the mother. Conversely, a notable proportion of fathers (26.7%) do not consider themselves a central figure in the management of the disease; some of these fathers identify the mother as the principal caregiver, with themselves assuming a more peripheral role. Other fathers indicate that their contribution is

primarily limited to providing emotional support regarding the disease, with less involvement in the practical management of the condition.

Do you feel that you actively contribute to managing your child's illness?

A large proportion of fathers (83.3%) report feeling that they actively contribute to the management of their child's disease, while a smaller group (16.7%) indicates that they contribute little or less than they would like. Some of these fathers further stated that it is primarily the mother who plays the dominant role in the management of the PKU.

Do you feel adequately informed about the illness?

In the majority of cases (83.3%), fathers reported feeling "adequately informed," although some expressed feeling poorly informed and uncertain about the disease's progression and future management. The remaining 16.7% indicated that they do not feel sufficiently informed about the characteristics of their child's condition. One father reported coping with this lack of information by independently seeking to supplement his knowledge through personal research despite having limited trust in self-directed learning in this area.

Do you feel in some way responsible for your child's illness?

The final question addressed the sense of responsibility that a father may feel, and nearly all fathers responded by considering responsibility in relation to the transmission of the disease, particularly its genetic component.

Regarding the responses, 70% of fathers indicated that they do not feel responsible for the transmission of the disease, while the remaining 30% expressed feelings of guilt for having genetically transmitted the condition to their children. Some of these fathers specified that they feel responsible despite acknowledging that it is not their fault and recognizing the impossibility of identifying the risk of transmission beforehand. One father, however, stated that he feels responsible for managing the disease but not for the transmission of PKU.

Correlations

Several correlations were observed between paternal engagement and both fathers' and children's psychological variables (Table 4).

Table 4. Correlation between paternal engagement and biochemical levels and fathers' and children's psychological functioning.

	Engagement TOT	Engagement "control"	Engagement "reference figure"	Engagement "disease management"	Engagement "information"	Engagement "responsibility"
Mean Phe	*r*=-0.222 *p*=0.248	*r*=-0.383* *p*=0.040	*r*=-0.353 *p*=0.060	*r*=-0.119 *p*=0.537	*r*=-0.159 *p*=0.410	*r*=0.086 *p*=0.658
IUS	*r*=-0.461* *p*=0.014	*r*=-0.223 *p*=0.253	*r*=-0.456* *p*=0.015	*r*=-0.280 *p*=0.149	*r*=-0.377* *p*=0.048	*r*=-0.172 *p*=0.382
PKU-QOL	*r*=-0.479* *p*=0.010	*r*=-0.417* *p*=0.027	*r*=-0.493* *p*=0.008	*r*=-0.429* *p*=0.023	*r*=-0.389* *p*=0.041	*r*=-0.128 *p*=0.517
PSI-SF	*r*=-0.490* *p*=0.006	*r*=-0.440* *p*=0.015	*r*=-0.470* *p*=0.009	*r*=-0.505* *p*=0.004	*r*=-0.317 *p*=0.088	*r*=-0.016 *p*=0.934
GAD	*r*=-0.328 *p*=0.077	*r*=-0.355 *p*=0.054	*r*=-0.357 *p*=0.053	*r*=-0.431* *p*=0.018	*r*=-0.051 *p*=0.791	*r*=0.108 *p*=0.570
PHQ	*r*=-0.303 *p*=0.104	*r*=-0.212 *p*=0.260	*r*=-0.384* *p*=0.036	*r*=-0.566* *p*=0.001	*r*=-0.005 *p*=0.979	*r*=0.166 *p*=0.381

*p-value < 0.05

Total paternal engagement was found to be moderately negatively correlated with parenting stress, child quality of life, and intolerance of uncertainty.

Specifically, moderate negative correlations were also observed between the engagement in control and both the parenting stress variable and children's quality of life. Engagement with the reference figure was negatively correlated with both the child's quality of life and intolerance of uncertainty, as well as with paternal stress.

Engagement in disease management showed moderate correlations with paternal depression symptoms and parenting stress. The final significant correlations were found between the engagement in information and both child quality of life and intolerance of uncertainty.

Linear regression

The linear regression model was used to test if predictors (mean Phe levels, total parenting stress score, and paternal engagement total score) could significantly predict the child's quality of life.

The results show that the independent variables significantly predict the child's total PKU-QOL score, F (3, 25) = 9.008, $p<0.001$, indicating that the model is significant. Furthermore, the Adjusted $R^2=0.480$ suggests that the model explains 48.0% of the variance in the dependent variable. Specifically, higher levels of parental stress are associated with a greater negative impact on the child's quality of life, while mean Phe levels and paternal engagement do not emerge as significant predictors. The main results of the regression model are reported in Table 5.

Table 5. Linear regression for children quality of life.

	PKU-QOL total			
	B	**Std. β**	**t**	***p*-value**
Intercept	17.227		1.424	0.168
Mean Phe	0.028	0.194	1.314	0.202
PSI total	0.261	0.463	2.877	0.009*
Engagement total	-0.418	-0.310	-1.976	0.060
Model fit	F (3, 25) = 9.008; $p<0.001$			
Adjusted R^2	0.480			

*p-value < 0.05

DISCUSSION

PKU is a condition that significantly impacts patients and their families, not only through the medical challenges of managing a strict low-Phe diet but also through the psychological burden it imposes, affecting emotional well-being, social dynamics, and overall quality of life. The management of PKU requires strict and continuous monitoring, and during childhood, the burden of managing the condition primarily falls on the caregivers. However, despite previous studies in other chronic illnesses highlighting the importance of both parents' involvement in a child's psychological well-being[22], the engagement of fathers in the care of children with PKU has been overlooked.

This study aims to examine the psychological functioning of children with PKU and their fathers, with a specific focus on the paternal perspective on their engagement in disease management.

The first objective was to assess the impact of the disease on the psychological well-being of children and fathers. The results confirmed, in line with the study of MacDonald et al[33], that PKU has a moderate impact on the daily life of children with this condition. This suggests that children with PKU can lead a largely fulfilling life, maintaining adequate levels of quality of life[34].

Regarding fathers, the literature presents conflicting evidence, partly due to the limited research focused on paternal well-being in caregiving. The findings of this study did not reveal any values outside the normative range for parenting stress, anxiety, or depression symptoms. These results are consistent with those of Fidika et al[10], which found that parents of children with PKU do not experience higher stress due to the condition; however, it contrasts with other studies that suggest a

psychological impairment resulting from the challenges of managing PKU[11,35]. Our results can be attributed to the medical and psychological support provided by the hospital's metabolic team, which includes various healthcare professionals, including psychologists. Addressing multiple aspects of the patients' and their families' needs can facilitate better adaptation to the condition and reduce stress, anxiety and impact on quality of life.

The second objective of this study was to analyze paternal engagement both quantitatively and qualitatively in order to explore the paternal perspective on their involvement in disease management.

From a quantitative perspective, fathers report relatively good levels of engagement across almost all aspects of engagement, except for the "responsibility" component; in this section, fathers were asked whether they felt responsible for their child's illness, and a large part of them stated that they feel little responsibility for their child's PKU. The quantitative results on paternal engagement seem to show that fathers perceived themselves as adequately engaged and involved in PKU management; these findings are in contrast with a study on diabetes, which highlighted fathers' tendency to assume less responsibility than mothers[23]. Despite that, a smaller but considerable group of fathers (16.7–33.3%) reported difficulties in different aspects of paternal engagement.

Qualitative analysis of open answers helped with a deeper investigation of fathers' points of view on their engagement. Coherent with previous quantitative analysis, a small number highlighted a high burden and difficulties in daily management that seemed to undermine their sense of involvement. In particular, almost a quarter of fathers (20–23%) expressed insecurity about the future progression of the disease, fear of losing control over managing disease-related tasks, and uselessness in practical and daily support; also, 10% expressed feeling that their parental role was secondary to that of the mother in disease management, with mothers taking on a more prominent role. In the responsibility component, fathers focused mainly on their responsibility regarding their guilt in the genetic transmission of the disease rather than their responsibility in managing their son's PKU: almost a third of them (30%) reported that they felt highly responsible for their child's PKU, and qualitative analysis permitted to deepen that this perception is due to the genetic transmission of the illness.

These results show that, despite the larger part of fathers reporting adequate levels of engagement, there is a smaller but considerable number of fathers who perceive themselves as unhelpful in daily support and that their role as parents is secondary to that of the mother in disease management. Moreover, they reported fear of losing control over disease-related tasks and guilt for the transmission of PKU. The responses are partially consistent with studies on other chronic illnesses that reported that fathers often perceive themselves to be less involved, more insecure and less satisfied due to difficulties in balancing illness management with work and personal responsibilities[21,35].

These findings highlight the need to give attention and further improve both practical and psychological support from the hospital team, with particular attention to involving both parents. As suggested by the studies of Phares et al[22] and Wysocki and Gavin[19], such involvement has positive consequences not only for behavioral factors, such as treatment adherence but also for a child's psychological well-being.

The third objective aims to analyze the correlations between paternal engagement and metabolic control, as well as the psychological variables of both children and fathers, in order to deepen the understanding of the relationship between these dimensions.

The results reveal a negative correlation between Phe level and the "control" component of paternal engagement perceived in relation to the child's illness. This suggests that the two components may influence each other, with a greater sense of fathers' control being associated with lower Phe levels. Since blood Phe levels reflect treatment adherence, it can be hypothesized that greater paternal involvement in managing the child's PKU may promote better therapy adherence. The findings of Wysocki and Gavin[19] support this result, highlighting that increased paternal involvement was associated with better maintenance of treatment adherence and a more favorable quality of life.

Moreover, it has been highlighted that higher levels of paternal involvement are associated with lower levels of parental stress, as well as fewer anxiety and depressive symptoms in fathers. These findings suggest that greater involvement of the father in managing the child and their illness is linked to better mental well-being and lower stress levels in the father. In particular, the father's sense of involvement in managing the child's disease appears to be an important factor, as it is related to all variables of the father's psychological well-being. Despite the literature on the relationship between these factors is largely limited, it appears that adequate paternal involvement in caring for the child's illness may serve as a protective factor against experiencing psychological distress in fathers themselves.

Moreover, higher levels of paternal engagement have been found to be associated with lower levels of intolerance to uncertainty in children and a reduced impact of the illness on their quality of life. These findings suggest that fostering strong paternal involvement can enhance the children's quality of life while also increasing their confidence in managing the uncertainty they may experience due to their condition. These results are consistent with studies that confirm that greater paternal involvement, alongside maternal involvement, promotes stronger family relationships, reduces perceived stress in the couple, and improves the quality of life for children with chronic illnesses[23,25].

The final goal of this study was to analyze the medical and psychological factors capable of predicting the child's quality of life. We expected, consistent with previous studies, that the medical and psychological factors of both the child and the father[11,33] significantly influence the quality of life of children with PKU. The results highlight that average Phe concentration, parental stress, and paternal involvement together are significant predictors of the child's quality of life.

A higher level of blood Phe is associated with a greater impact of PKU on the patient's quality of life, as it may lead to a sense of failure due to non-adherence to treatment and foster negative thoughts about the disease, preventing the child from feeling equal to their peers. Although the medical component has an important impact, parental-related variables are even more determinant: parental stress and paternal involvement emerge as the most influential predictors of the child's quality of life.

Indeed, higher levels of paternal involvement and lower father's parenting stress are predictive of a better child's quality of life; as a matter of fact, stress and engagement are closely interrelated and together influence the child's psychological well-being. An absent father may struggle to manage the disease effectively or to adopt effective coping strategies to address the challenges associated with the condition[36]. A father who is adequately involved in taking care of his child with PKU and perceives less stress in managing the condition seems to be able to ensure a higher level of psychological well-being for the child, potentially mitigating the negative impact of the disease.

Based on these results, and consistent with previous studies[23], the importance of further exploring the father's role in the family balance of families with children affected by chronic conditions becomes crucial. Fathers prove to be fundamental resources not only for disease management but also for reducing the impact that a chronic condition such as PKU may have on the child's quality of life.

Limitations

In our study, we investigated paternal engagement among fathers of children with various forms of PKU. Future research could explore potential differences across PKU subtypes, considering that different forms of the condition may necessitate distinct therapeutic approaches, which, in turn, may influence coping mechanisms and psychological challenges faced by parents.

Additionally, an *ad hoc* questionnaire was employed to assess paternal engagement. While this choice was driven by the need for a brief condition-specific instrument suitable for fathers of children with PKU, the use of a non-standardized measure poses limitations. Specifically, it complicates comparisons with normative populations and may reduce the generalizability of the findings.

CONCLUSIONS

This study demonstrated that fathers of children with PKU perceive themselves as not experiencing significant psychological distress and feel generally adequately involved in the management of the disease. However, some fathers reported feeling responsible for transmitting the genetic mutation causing PKU to their child, feeling less helpful in managing the disease-related issues, and perceiving their parental role as secondary to that of the mothers. Moreover, it was shown that greater paternal involvement may contribute to better metabolic control, improved quality of life, and reduced intolerance to uncertainty in the children, as well as being a protective factor for the fathers' own mental health.

These findings suggest that increasing paternal involvement in the management of pediatric PKU, given the challenges and burden it places on the entire family, may promote the child's well-being, both in terms of treatment adherence and the child's psychological health.

Clinicians should, therefore, ensure greater attention to the paternal role in disease management, from the time of diagnosis through to daily PKU treatment.

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Study conception and design: G.G, A.G.; collection and interpretation of data: G.G, A.G.; statistical analysis: G.G.; manuscript drafting: G.G, A.G.; manuscript editing: G.G, A.G.; approval to submit: G.G, A.G.

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AUTHOR CORRECTION - NEWBORN SCREENING, DIAGNOSIS, AND MANAGEMENT OF INHERITED METABOLIC DISORDERS: STATUS AND PROGRESS OF THE SOUTHERN MEDITERRANEAN COUNTRIES

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