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ORIGINAL RESEARCH

Patient journey in cystinosis: focus on non-adherence and disease management

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Abstract

Background: Few studies have assessed patient-reported experience measures in nephropathic cystinosis. This study uses patient reports focused on the impact of cystinosis, cysteamine treatment-associated problems, and therapeutic adherence and suggests potential actions for improvement.

Methods: In March 2022, six patients with nephropathic cystinosis treated with cysteamine, aged between 12 and 40 years as well as two caregivers, underwent standardized online interviews. Further, in April 2022, two online workshops were organized, each one with the participation of an advisory board consisting of up to four patients and six caregivers. As a result, the first patient journey mapping was developed considering pre-diagnosis, diagnosis and post-diagnosis steps, prescription of treatment, laboratory tests and daily life for patients, categorized by age (children, teenagers, adults). A patient support programme was also considered.

Results: Patients were not completely aware of the risks associated with non-adherence. The main factors explaining poor adherence were impaired sleep and chronic fatigue, both related to cysteamine night dosing and prominent gastrointestinal symptoms. These factors have a negative impact on the daily lives of patients. Opportunities for improvement in disease management and therapeutic adherence in nephropathic cystinosis were highlighted. Consequently, a series of lines of action and suggestions were made.

Conclusion: This qualitative study offers insights on nephropathic cystinosis from the point of view of patients and parents/caregivers. The critical steps during patient journey and the pitfalls for therapeutic adherence have been highlighted, opening ways to improve not only disease management but also the quality of life of patients with cystinosis.

A lay summary is provided as supplementary material; available at: https://www.drugsincontext.com/wp-content/uploads/2024/10/dic.2024-7-1-Suppl-Lay-Summary.pdf

Keywords: adherence, cysteamine, cystinosis, patient journey, PREM, qualitative research.

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Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disease with an incidence of 1/100,000–200,000 live births, although there is a wide variety worldwide.[1] It is characterized by lysosomal cysteine accumulation as cystine crystals throughout the body, leading to kidney, bone, ocular and other systemic symptoms.[1,2] It usually manifests in infancy as renal Fanconi syndrome and, without a specific treatment, would lead to renal failure at the end of the first decade.[2] Cystinosis is caused by biallelic mutations of the *CTNS* gene on chromosome 17p13.2. More than 140 pathogenic *CTNS* mutations have been reported in patients with cystinosis worldwide up to 2019.[3]

Treatment with cysteamine has changed the outcome of cystinosis. Early initiation of cysteamine therapy improves prognosis of the disease,[4] with better renal function in comparison to patients with later onset of therapy.[5] Long-term cysteamine treatment is associated

with a reduction in frequency and severity of extra-renal complications, improved growth, and increased survival.[6] However, despite non-adherence being known to be related to kidney disease progression and reduced life expectancy,[7] adherence is poor in many patients because of the adverse effects of cysteamine and its strict dosage amongst other factors.[7,8]

This study assesses the impact of cystinosis and treatment-associated challenges on therapeutic adherence to detect potential leverages of change and propose lines of actions based on patient-reported experience measures (PREMs).

Methods

Setting and design

The patient experience framework used in this article is built upon WHO's[9,10] definition of health, considering physical, mental and social well-being. Emotional impact, social determinants and cultural influences are crucial.[10–13] The healthcare system provides the context, extending to various life aspects. The patient model includes five dimensions: physical health, healthcare interactions, emotions, social dynamics and cultural symbolism, all shaping patient experience. This approach was applied herein to nephropathic cystinosis. A qualitative research study was designed using a methodology that allowed the assessment of the five dimensions. The study, conducted by the Instituto Experiencia Paciente, comprised individual interviews and workshops.

Participants

Participant recruitment was achieved through Grupo Cistinosis, the Spanish cystinosis patient association. Inclusion criteria were age between 12 and 40 years, diagnosed with nephropathic cystinosis and receiving cysteamine; caregivers of patients younger than 15 years of age were also included. Exclusion criteria were not necessary. Participating patients were two children, two teenagers and two adults with nephropathic cystinosis aged between 12 and 40 years. Five patients were male and one was female. All patients were receiving a maintenance dose of cysteamine bitartrate. Paediatric patients were receiving delayed-release cysteamine, whilst teenagers and adult patients were on immediate-release cysteamine.

Interviews and workshops

In March 2022, standardized open in-depth interviews were conducted via Google Meet (Google Ireland Ltd, Dublin, Ireland). Interviews lasted 45–60 minutes; they were designed by the Instituto Experiencia Paciente – IEXP (Madrid, Spain) and guided by interview and listening scripts previously developed and validated.

In April 2022, two online 2-hour participatory health research workshops were performed via Zoom (Zoom Video Communications, Inc., San Jose, CA, USA) to validate and confirm the results of the previous interviews. Workshop contents were based on interview results and issues of interest. Each workshop was attended by an advisory board consisting of patients with nephropathic cystinosis and caregivers. Patients and caregivers were those who already participated in the interviews. The first workshop was devoted to assessing the disease impact on daily life, disease management and barriers to adherence, follow-up and involved specialists, and integral healthcare approach to patients with nephropathic cystinosis. The participants were two teenage patients, two adult patients, four caregivers and one facilitator. The second workshop aimed to construct the patient's journey during childhood, adolescence and adulthood. Participants were two teenage patients, one adult patient, four caregivers (of paediatric patients) and one facilitator, as well as two caregivers who participated spontaneously with the teenage patients. During both workshops, facilitators used a Miro whiteboard (RealtimeBoard Inc., dba Miro, San Francisco, CA, USA) to record the main insights.

Development of patient journey mapping

Following the interviews and workshops, patient journey mapping (PJM) was developed. This instrument systematically examines the trajectory and experience of patients in relation to a disease, a treatment or a healthcare system.[14] In this project on nephropathic cystinosis, the PJM included the following phases: pre-diagnosis, diagnosis, post-diagnosis, prescription of treatment, environmental awareness, transition to adult healthcare circuit, follow-up, laboratory tests and daily life. For each phase, results included patient beliefs and thoughts, actions and events, contact points with healthcare system, and caregivers' emotional curve. Those phases corresponded to childhood, adolescence and/or adulthood stages of a patient's life. Adherence-related factors and actors involved in the PJM were also examined.

Applicability of study results

A patient support programme (PSP) was assessed and applicability of study results was defined, with proposed lines of action and suggestions.

Ethics statement

The study was performed according to the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Personal data were anonymized by following the guidelines specified in Spain's data protection regulations. All participants in the study (patients and their caregivers) received verbal and written information about the procedures and

objectives of the study and signed an informed consent form before their inclusion. The participants under the age of 18 assent to participate but the informed consent was signed by their parents. Personal data were anonymized by following the current European General Data Protection Regulation (GDPR, 2016/679) and related Spanish Law (3/2018). Approval of an Ethics Committee was not necessary because the study was qualitative research based on interviews and workshops (Real Decreto 957/2020, November 2020). The study is compliant with Equator Network Guidelines (Supplementary Table 1, COREQ checklist; available at: https://www.drugsincontext.com/wp-content/uploads/2024/10/dic.2024-7-1-Suppl-Table-1.pdf).

Results

Patient journal mapping

Below, we describe the main findings of the PJM for nephropathic cystinosis categorized by patient age (Table 1).

Childhood

Pre-diagnosis

Pre-diagnosis phase was assessed from the perspective of caregivers using patient-proxy reports, as the study patients had an early disease onset, in all cases during the first months of life. Onset of symptoms was a crucial moment for parents and caregivers, representing a breakup from 'normal' parenthood experience. First symptoms were vomiting, polyuria, polydipsia and secondary rickets, leading to early involvement with the healthcare system and long hospitalizations.

The more frequent diagnosis was Fanconi syndrome. Some patients had an incorrect initial diagnosis but were referred to reference specialists afterwards. Time frame from the initial symptoms to diagnosis of cystinosis extended between 2 and 3 months.

Diagnosis

Most of the interviewed patients were diagnosed between 6 and 8 months of age; therefore, this phase was assessed by parents/caregivers. Diagnosis phase represented a critical point as parents/caregivers had to face a rare disease confirmation and its impact on daily life. They reported uncertainty, ignorance, fear and lack of information after diagnosis. As they did not recall receiving adequate information about the disease, they were not aware of the impact of the diagnosis of cystinosis on patient outcomes.

After diagnosis

During the post-diagnosis phase, parents/caregivers began to deal with cystinosis. Although the lack of information persisted, they started to accept the diagnosis and looked for information, initially through the Internet and subsequently with healthcare providers specialized in cystinosis. Furthermore, they made contact with patient associations.[15]

Treatment and adherence

The treatment phase was divided into two main stages. The first stage involved the first years of life, a critical period because of the adverse events associated with drug therapy and the disorganization of schedules and dosages. The second stage began at the time that the disease and its treatment were addressed. At the onset of treatment, parents/caregivers did not have enough information on different drugs and their effects. Moreover, they reported a poor organization, with impaired patient and parents'/caregivers' schedules and a feeling of 'chaos'. In addition, the first years of treatment were reported as a complicated time because of disease symptoms and treatment-related adverse events. Parents/caregivers felt frustrated, they did not perceive an improvement and even noticed impairment after treatment. Moreover, there was a concern about the many drugs used and the lack of information.

Non-adherence was not observed in childhood because parents/caregivers were in charge of treatment. However, young patients become progressively involved in the management of their disease, being aware of the relevance of adherence, participating in the organization of their treatment and being informed of the potential adverse events.

Environment awareness, mainly in family and school, was also part of the PJM. Relatives and teachers were aware of not only the disease and its treatment but also the occasional discomfort that the patients could suffer.

The breakup of routine and social life was reported by patients and their parents/caregivers. During childhood, parents/caregivers were in charge of night dosage and their sleep was disturbed. Additionally, treatment impairs social life of both patients and their parents/caregivers.

Follow-up

Regarding laboratory tests and follow-up visits, patients and caregivers sometimes report non-satisfactory relationship with healthcare professionals and unsuitable schedules for blood extraction for children.

As for cystinosis follow-up, treatment follow-up is multidisciplinary and multiple visits to different specialists are needed. Therefore, patients and their parents/caregivers spend considerable time with medical visits and frequently need to travel to distant reference centres because there is no specialist near them. However, sometimes healthcare

Table 1. Patient journey: main results by phase and age of patients.

Phase	Age of patients	Findings
Pre-diagnosis	Childhood	• First symptoms • Wrong diagnoses • Early involvement with healthcare system and long hospitalizations
Diagnosis	Childhood	• Uncertainty, fear • Lack of information
After diagnosis	Childhood	• Beginning of acceptation of the diagnosis • Lack of information • Contact with patient associations

Treatment	Childhood	• First years of treatment
		  • Treatment-related adverse events
		  • Disorganization of schedules and dosages
		  • Frustration
		  • Lack of information

Adherence	Childhood	• Non-adherence was not observed
	Adolescence	• Patients wanted to be more in charge of their treatment • Intermediate phase between adolescence and adulthood with temporary non-adherence
	Adulthood	• Non-adherence related to travels or long-lasting events and to unilateral dosage modifications
Environmental awareness	Childhood	• Relatives and teachers know the disease, its treatment and the occasional discomfort
	Adolescence	• Patients want to be 'normal' and try to hide their condition
Transition and transfer to adult healthcare circuit	Adolescence	• Critical period, potential problems
Follow-up	Childhood	• Multiple visits, sometimes coordinated • Distant reference centres
	Adulthood	• Null or very little knowledge of the disease by healthcare providers
Laboratory tests	Childhood	• Non-satisfactory relationships with healthcare professionals and unsuitable schedules for blood extraction
Daily life	Childhood	• Breakup of routine and social life

providers try to co-ordinate visits or use electronic mail to resolve doubts.

Adolescence

Adolescent patients do not feel considerably identified with the disease, wanting to be 'normal'; therefore, they usually try to hide their disease, yet it is difficult to conceal the complex medication from their friends and classmates. Furthermore, they were concerned by their low height and muscular development, as well as their physical appearance and body image issues. However, some of them finally accepted their differences.

Adherence

Change from childhood to adulthood occurs not only within the healthcare circuit but also in daily life. Adolescent patients want to be more in charge of their treatment. Nevertheless, it is sometimes difficult to maintain adherence. Although parents/caregivers closely supervise the treatment, the daily life of adolescents overcomes strict schedules of medication.

Follow-up: moving into adulthood

Transition and transfer from paediatric to adult healthcare circuits can be a problem. It is a time of uncertainty,

with new health professionals, who are unknown to patients and their parents/caregivers.

Adulthood

Adherence

Between adolescence and adulthood, there is an intermediate phase that could be named the independent youth. Interviewed adult patients explained that they discontinued their treatment during this phase, with total withdrawal or systematic incompliance with cysteamine dosage. Later, in adulthood, patients resumed the treatment because of physician pressure or advice, present and future disease worsening, threat of death and best harmonization of dosage with daily life.

However, systematic non-adherence issues were detected during interviews, mainly due to a lack of planning and convenience, such as during travel or assistance to long-lasting events, and unilateral dosage modifications, especially related to night doses.

Follow-up

Healthcare providers in charge of adult patients with cystinosis have null or very little knowledge of the disease. As a result, patient follow-up is not appropriate; nephrologists cannot persuade patients and caregivers to comply with the prescribed dosage, and there is a lack of instruments to increase disease awareness in adult patients.

Impact of cystinosis on the lives of patients

During the first workshop, patients and caregivers reported the symptoms and treatment-related issues that were most interfering with daily life (Table 2). Sleep interruption and fatigue were recalled as the most troublesome and were considered the main factors to understand the experience of patients with cystinosis. Extra-renal affections were also relevant.

Adherence

At the first workshop, patients and parents/caregivers were also asked to classify 15 elements according to the number of times they affected the dosage: never, rarely, sometimes or almost always (Table 3). Medication packaging type never affected the dosage in parents/caregivers that prepared treatment for takeaway, neither in most adult patients. Instead, sleep discontinuation and falling asleep were the main causes of non-adherence, followed by gastrointestinal discomfort, mainly vomiting.

Table 2. Impact of nephropathic cystinosis and its treatment on daily life of patients and parents/caregivers.

Greater impact	• Fatigue and sleep interruption (related to treatment)
	• Skeletal and neuromuscular complications
	• Ocular complications
	• Failure to thrive and muscle development
	• Body odour and halitosis (related to treatment)
	• Photophobia
Less impact	• Thirst

Patient support programme

Healthcare professionals involved in the PSP were a nephrologist, an ophthalmologist, a nutritionist, a nurse, an endocrinologist, a neurologist, a pulmonologist, a physiotherapist and a psychologist. A mapping of actors in the PSP was created, with four levels of contact. In Level 1, the actors are closer to the patient (parents/caregivers). In Level 2, there are actors of reference who are close to the patient: a nephrologist, with visits at intervals of 2–3 months, and associations of patients. In Level 3, there were healthcare providers of reference with contact at least every 2 months: a neurologist with visits every 6 months, an ophthalmologist with visits every 3–6 months, and a nutritionist with visits every 1–3 months. Finally, Level 4 comprises nurses, a psychologist with monthly visits (although not all patients and caregivers consider these professionals particularly useful), an endocrinologist every 3 months, and a physiotherapist (uncommon).

Proposal of a comprehensive service for follow-up and care of patients with nephropathic cystinosis

Patients exposed their opinions on the ideal characteristics of a comprehensive service for follow-up and care of nephropathic cystinosis (Box 1). The goal was to increase the quality of life by means of a multidisciplinary approach.

Table 3. Barriers to adherence in patients with nephropathic cystinosis treated with cysteamine.

Never affects adherence	Rarely affects adherence	Sometimes affects adherence		Almost always affects adherence
Container format	Needing water	Ability to play sports	Fast before/after meals to take medication	Waking up to take the medication
To take pills in front of others		Leisure time	Gastrointestinal effects	Falling asleep
		Preparing medication for a trip	Vomiting	
			Halitosis	

Box 1. Main characteristics of a comprehensive service for follow-up and care of nephropathic cystinosis from the perspective of patients and parents/caregivers.

- Cystinosis-specialized health professionals
- Visits unified in 1 day
- Good and personal communication between multidisciplinary healthcare professionals
- Use of telemedicine
- Professionalized telematics channels

Applicability of the project results to a multidisciplinary PSP environment and adherence

After a global analysis of project results, we identified the main barriers, limitations, preferences and motivators of patients for maintaining adherence to cystinosis treatment. Consequently, we assessed opportunities and developed lines of action and suggestions for improvement of healthcare circuit (Table 4) and adherence (Table 5). All these data can be the basis for the implementation of a *Project Adherence in Rare Diseases: Nephropathic Cystinosis.*

Discussion

We assessed therapeutic adherence and disease management in nephropathic cystinosis using a qualitative methodology with participation of patients and parents/caregivers. It is an example of participatory health research, which involves all the actors related to a disease, procedure, and so on. This type of research is increasingly relevant.[16]

PJMs were developed using key features of standardized patients and made based on PREMs and caregiver-reported experience in nephropathic cystinosis and not from that of the healthcare providers. PJMs are useful to gather barriers and motivators, especially in critical moments or phases of the patient experience. They also allow the mapping of the touchpoints between healthcare providers and the patients and exploration of opportunities for improvement. The main value of PJMs is their ability to arrange information obtained from complex experiences.[14] Patient journey method has been applied to other lysosomal storage diseases,[17] such as Gaucher disease[18] and Fabry disease,[19] as well as to other rare diseases such as congenital adrenal hyperplasia.[20] The final aim is always to improve the healthcare of patients with rare diseases.

This study provides new data related to PREMs in nephropathic cystinosis in comparison to previous 'traditional' research. The most remarkable finding is related to adherence to cysteamine. Adherence was found to be reduced in adolescent and adult patients, but it was good in children.[7] Herein, data indicated that adherence are sub-optimal at any age, including children. Parents and caregivers are aware of the disease and the risks derived from non-adherence; therefore, they follow the prescribed schedule and dosage. However, children are not really aware of the risks of non-adherence and, if left on their own, they could be non-adherent. Surveillance by parents/caregivers is the key for maintaining adherence in children, and it can be helpful in teenagers. In

Table 4. Applicability of results: improvement of healthcare processes.

Applicability	Lines of action	Suggestions
Information against uncertainty	Create networks of specialists in front of a first case of cystinosis through scientific societies Create networks between caregivers and patients both newly diagnosed and with long-term disease	Reinforce synergies of patient associations Co-ordinate measures with them
Internet as information facilitator	Create forums with contrasted information Promote true information	Create an online community of patients and healthcare professionals Include educative and scientific material useful for patients and caregivers
Implementation of emotional support		
In front of uncertainty	Create support groups	Implement online community of patients and caregivers
Help with physical appearance issues	Increase awareness by patients and free them from blame	Health coaching
Schedule adaptation for laboratory tests during follow-up	Write a short report for nurses with some indications Raise awareness of nurses on the importance of timely laboratory tests	Organize participative healthcare workshops with patients and health workers
Less in-person visits	Unify visits in 1 day	Offer telematics visits if possible Home delivery of medication
Improvement of communication between specialists		

turn, both teenagers and adults reported that they understood the importance of cysteamine treatment and the risks of non-adherence. However, as expected, they discontinued cysteamine or did not take doses on purpose, many times for apparently trivial reasons such as social events. The transition from paediatric to adult care is a critical time. A coordinated model has already been suggested,[21] and the applicability of the study results could be added to this model.

Delayed-release cysteamine could help to increase adherence.[22] Research has shown that one of the main problems for treatment adherence is the number of doses and night-time dosing.[7] As delayed-release cysteamine addresses this issue, it could be an important factor to increase adherence. However, in this study, all adolescent and adult patients were being treated with immediate-release cysteamine; therefore, no potential differences in adherence between the cysteamine formulations could be assessed.

Poor adherence to cysteamine can be due to gastrointestinal adverse events[8] as also found herein. Nevertheless, we also recorded sleep disturbance and fatigue, both problems related to cysteamine night dosing, as the most important barriers to adherence. It may be useful to conduct a study involving patients treated with delayed-release or immediate-release cysteamine and their parents/caregivers.

Amongst the many results of this study, we selected those that we considered to have fast applicability and classified them into two groups: improvement of healthcare processes and improvement of therapeutic adherence. Lines of action and suggestions were developed for each of the selected results that were considered as opportunities to change the current state of adherence and disease management.

The European Rare Kidney Diseases Reference Network (ERKNet) also studied the patient journey in cystinosis.[23] Compared with the present PJM, the ERKNet patient journey only had five phases (first symptoms, diagnosis, more symptoms, treatment and surgery, and adulthood). It was presented as a chart, with clinical manifestations, diagnosis and treatment clearly explained, but the results

Table 5. Applicability of results: improvement of adherence.

Stage of life	Applicability	Lines of action	Suggestions
General	Treatment organization	Promote doubt-solving by health professionals Promote communication between specialists treating patients with cysteamine	Online workshops 'patient-centred prescription'
	Faced with the feeling of 'non-improvement' reported by caregivers at the beginning of treatment with cysteamine	Specialized planning Educate healthcare professionals Promote active listening and understanding	Online platform Guidelines with appropriate instruments and online education
Childhood	Facilitate support during school hours	Provide external help to families	Collaboration with schools, counselling on state aids
Adolescence	Adherence in adolescence to promote it in adulthood	Coaching and support groups Provide clear information on the risks of non-adherence	Health coaching for patients and caregivers Educative material for children
	Tools to deal with being on treatment	Provide tools to manage emotions and social interactions	Health coaching
Adulthood	Use of nephrology services as anchor points	Increase disease awareness in nephrologists for adults	Involvement of scientific community
	Help for planning some situations	Coaching and motivation of patients Reduce or modify packaging	
	Empowerment of specialists to defend dosage	Educate specialists	Create an online community
	Control of the affected population	Use of a PREM such as the modified IEXPAC and a PROM for rare diseases	

IEXPAC, Instrument for Assessing Patient Experience of Chronic Illness (according to its abbreviation in Spanish); PREM, Patient Reported Experience Measure; PROM, Patient Reported Outcome Measure.

were less detailed. However, both PJMs highlighted the need for a multidisciplinary team, the critical period of transition to adulthood and the relevance of information to parents/caregivers and patients.

This study has two main limitations: its qualitative nature, which could make the generalization of its results difficult,[24] and the apparently small sample size. However, qualitative research seeks a sample size large enough to provide an in-depth understanding of a phenomenon until data saturation is reached. As of 2023, there are 65 people in Spain diagnosed with nephropathic cystinosis; therefore, the participation of 6 patients equates to 9.23% of the total population and is a highly representative number.

However, the study methodology was focused on finding the key points of medical and social experiences of patients and their parents/caregivers. Consequently, we have been able to gather relevant information on cystinosis experience, particularly on its management and adherence to cysteamine therapy. Therefore, the main strength of this study is the finding of the main themes and issues that are relevant to patient experience through qualitative research and patient/caregiver participation through workshops. Further quantitative research based on the findings and insights is needed.

Conclusion

This qualitative study offered insights on the treatment of nephropathic cystinosis from the point of view of patients and their parents/caregivers. The critical moments in the patient journey and the pitfalls for therapeutic adherence have been highlighted, opening ways to improve not only healthcare but also the quality of life of patients.

Contributions: All authors made significant contributions to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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