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Characterizing Families of Pediatric Patients with Rare Diseases and Their Diagnostic Odysseys: A Comprehensive Survey Analysis from a Single Tertiary Center in Korea

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Purpose: Rare diseases necessitate consistent access to specialized health services. In Korea, despite the growing socioeconomic burden, insufficient comprehensive research is available on patients with rare diseases and their families, particularly concerning factors influencing the length of time to diagnosis. The aim of this study was to thoroughly characterize rare pediatric diseases and explore factors impacting the diagnostic odyssey.

Methods: The study enrolled patients under 15 years old seeking medical care at the Seoul National University Children's Hospital Rare Disease Center between January 2022 and December 2023. Participating patients were required to have been diagnosed with one of the 1,248 rare diseases recognized in Korea. A 33-question survey was developed to assess clinical features of the patients, characteristics of their primary caregivers, and their perceptions of ongoing medical care.

Results: The study included 101 patients and their families. Regarding perceived cognitive and motor functions, most families indicated moderate or severe limitations (cognitive, 62.4%; motor, 57.4%). Over half of the families (53.5%) reported discontinuing employment to provide patient care. Neurological symptoms represented the most common initial chief concern, with dermatologic symptoms and laboratory test abnormalities also noted. Three factors were associated with time to diagnosis: the number of hospitals visited, whether the districts of residence and diagnosis aligned, and the age at symptom onset.

Conclusion: The comprehensive characterization of patients with rare diseases and their families in Korea, along with the identification of factors impacting the diagnostic odyssey, provides key insights for the development of a tailored support system.

Keywords: Rare disease; Delayed diagnosis; Socioeconomic factors

Introduction

Rare diseases are often characterized by their complexity, their chronic nature, and the potential for intellectual and physical disabilities, necessitating regular and sustained access to a variety of specialized health services [1]. The complexity of these conditions makes timely and accurate diagnosis crucial for affected families. Such a diagnosis enables them to clearly explain their child's medical condition to others, cease blaming themselves for their child's health issues, potentially restore reproductive confidence, and alleviate the stress associated with uncertainty about the illness and future expectations. In contrast, delayed or incorrect diagnosis can lead to the use of inappropriate and potentially harmful treatments [2-4]. However, the journey to diagnose rare diseases is often prolonged, as noted in numerous studies. A European study reported that 25% of patients with rare diseases faced a diagnostic odyssey lasting between 5 and 30 years [5], a finding echoed by an Australian study in which many patients experienced a period of over 5 years before diagnosis [6]. Advances in genomics have substantially shortened the diagnostic odyssey for rare diseases [7], but concerted efforts are still required to establish a comprehensive diagnostic framework [8]. In the United States, the National Institutes of Health initiated a program titled "Multidisciplinary machine-assisted, genomic analysis and clinical approaches to shortening the rare diseases diagnostic odyssey" with the aim of reducing the time to diagnosis for patients with these conditions [9].

Numerous rare diseases exist globally, with nearly 8% of the general population having such a condition, underscoring their impact despite their individual rarity [10]. A recent study estimated that 5.5 million children and adults in the United States are affected by rare diseases, resulting in a cumulative economic burden of $997 billion. This figure includes $449 billion (45%) in direct medical costs, $437 billion (44%) in indirect costs, $73 billion (7%) in non-medical costs, and $38 billion (4%) in healthcare expenses not covered by insurance [11]. In Korea, a rare disease is defined by the Rare Disease Act of 2016 as one that affects fewer than 20,000 patients or has an indeterminate prevalence due to its rarity [12]. A study by Choi and Lee [13] reported that from January 1 to December 31, 2020, Korea had 52,069 documented cases of rare diseases, with 691 distinct conditions. Patients diagnosed with these diseases incurred an average of 3,000 US dollar (USD) in expenses within the first 3 months after diagnosis [13].

Despite the considerable and increasing socioeconomic burden in Korea, the literature does not yet include a comprehensive characterization of patients with rare diseases and their families, nor an identification of factors influencing the duration of the diagnostic journey. The objectives of this study were to comprehensively characterize the clinical features and diagnostic odyssey of pediatric patients with rare diseases and their families, identify factors influencing the time to diagnosis, and assess their satisfaction with medical care.

Materials and Methods

This study enrolled patients under the age of 15 years who sought medical attention at the Rare Disease Center of Seoul National University Children's Hospital between January 2022 and December 2023. Under the inclusion criteria, patients were required to have been diagnosed with one of the 1,248 rare diseases designated by the Korea Disease Control and Prevention Agency, according to the International Classification of Diseases, 11th revision [14]. Patients with one of these diseases who planned to visit our clinic were screened the day before the visit, and their caregivers were asked about their willingness to participate in our survey. After informed consent was provided, a written survey was provided. The survey consisted of 33 questions designed to evaluate the clinical attributes of patients, characteristics of the primary caregiver, specifics of the disease, and perceptions of the ongoing medical care. The primary caregiver of the patient was asked to fill out the survey. Respondents were queried about the perceived cognitive and mobility status of the patient, with potential responses of "no limitation," "moderate limitation," and "severe limitation." No objective tests were performed to verify the cognitive and mobility statuses reported by the participants. The patient's residential district and the district where the diagnosis was made were recorded to understand the factors affecting the diagnostic odysseys of these patients. The "diagnosed district" was defined as the city or province where the hospital that provided the final diagnosis was located. For further analysis, patients were categorized based on whether their residential and diagnosed districts were the same or different. The number of hospitals visited before arriving at the institution that issued the final diagnosis was also recorded. This was referred to as the "number of hospitals visited" in the analysis. Both the Korean and English versions of the survey are available in Appendix 1. We also conducted a chi-square analysis to investigate factors influencing the duration of the diagnostic odyssey in pediatric patients with rare diseases. The patients were divided into two groups based on the time to diagnosis: those with diagnostic durations of less than 6 months and those with durations exceeding 6 months. The questionnaire was developed using key questions generated by the Seoul National University Hospital Rare Disease Center.

Data analysis was conducted using GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA). Categorical data were analyzed using either the chi-square or Fisher exact test, while

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continuous data were assessed with the Student t-test. Multiple logistic regression analysis was employed to identify factors associated with the duration of the diagnostic odyssey and the families' satisfaction with the medical care received. The study received approval from the Seoul National University Hospital Institutional Review Board (H-2209-143-1362).

Results

1. Clinical characteristics of families of pediatric patients with rare diseases

A total of 101 patients and their families were enrolled in the study. The largest group of patients were between the ages of 0 and 3 years (n=31, 30.4%), with the smallest group being those aged 7 to 9 years. When asked about the perceived cognitive function of the patients, 38 families (37.6%) reported no cognitive limitations, 59 families (58.4%) indicated moderate limitations, and four families (4.0%) described severe limitations. Regarding perceived mobility status, 43 families (42.6%) indicated no limitations, 37 families (36.6%) reported moderate limitations, and 21 families (20.8%) described severe limitations. The onset of symptoms most frequently manifested as developmental delay (n=28, 27.7%), followed by developmental regression and abnormal physical findings during examination (n=27, 26.7%) and congenital abnormalities (n=15, 14.9%). Most patients experienced the onset of symptoms before reaching 1 year of age (n=71, 70.3%). The most common primary phenotype associated with the final diagnosis was neurological (n=50, 49.5%), followed by muscular (n=19, 18.9%) and neurocutaneous (n=10, 9.9%). The primary caregivers for the patients were overwhelmingly mothers (n=93, 91.2%), and more than half of the families (n=54, 53.5%) reported that a member had stopped working to care for the patient. The clinical characteristics of the patients and families are summarized in Table 1. The diagnoses of the 101 patients included in this study can be found in Supplementary Table 1.

2. Diagnostic odysseys of families of pediatric patients with rare diseases

Patients predominantly sought initial medical attention at local hospitals (n=38, 37.6%) at the onset of symptoms. Secondary or tertiary hospitals were the next most common choice (n=33, 32.7%), followed by emergency rooms (n=30, 29.7%). Over half of patients (n=53, 52.5%) received a diagnosis within 6 months of their initial hospital visit, while 32 patients (31.7%) experienced a diagnostic odyssey lasting over a year. Before arriving at a conclusive diagnosis, a large proportion of patients (n=80, 79.2%) visited two to three different hospitals. The distribution of medical costs

Table 1. Clinical characteristics of pediatric patients with rare diseases and their families

Patients	No. (%) (n=101)
Sex	
Male	49 (48.5)
Female	52 (51.5)
Age at time of study (yr)	
0–3	31 (30.4)
4–6	22 (21.6)
7–9	20 (19.6)
≥10	28 (28.4)
Perceived cognitive function	
Not limited	38 (37.6)
Moderately limited	59 (58.4)
Severely limited	4 (4.0)
Perceived mobility	
Not limited	43 (42.6)
Moderately limited	37 (36.6)
Severely limited	21 (20.8)
Presenting symptom	
Developmental delay	28 (27.7)
Developmental regression/abnormal physical findings during examination	27 (26.7)
Congenital abnormality	15 (14.9)
Visual/hearing impairment	10 (9.9)
Skin lesion	9 (8.9)
Intrauterine abnormality	8 (7.9)
Seizure	4 (4.0)
Age at onset	
Before 1 month	38 (37.6)
1 month to 1 year	33 (32.7)
≥1 year	30 (29.7)
Primary phenotype of final diagnosis	
Neurological	50 (49.5)
Muscular	19 (18.9)
Neurocutaneous	10 (9.9)
Metabolic	8 (7.9)
Ophthalmologic	8 (7.9)
Others	6 (5.9)
Families	101
Primary caregiver	
Father	8 (7.8)
Mother	93 (91.2)
Educational status	
No higher education	15 (14.9)
Completed undergraduate education	75 (74.3)
Completed graduate education	11 (10.8)
Left a job for patient care	
Yes	54 (53.5)
No	47 (46.5)
Monthly income (USD)	
<3,000	28 (27.7)
3,000–5,000	44 (43.6)
≥5,000	29 (28.7)

USD, US dollar.

incurred before diagnosis was relatively even across three categories: less than 1,000, 1,000–3,000, and 3,000 USD or more. However, post-diagnosis, nearly half of the patients (n=45, 44.6%) reported expenses exceeding 3,000 USD for ongoing care. Among the 101 patients and families participating in the study, 43 patients were from Seoul or Gyeonggi province, making up 42.6% of the cohort. The remaining 58 patients hailed from various other provinces across Korea, constituting 57.4%. The residential distribution of the patient population closely mirrors the distribution of the general population in Korea [15]. The details are summarized in Table 2.

Our analysis of factors influencing time to diagnosis revealed a statistically significant correlation between the duration of the diagnostic odyssey and the number of hospitals visited. Specifically, among patients with a diagnostic odyssey shorter than 6 months, 51 visited two to three hospitals, two visited four to five hospitals, and no patients visited six or more hospitals. In contrast, within the patient group experiencing an odyssey longer than 6 months, 29 patients visited two to three hospitals, 13 visited four to five hospitals, and six visited six or more hospitals (P<0.001) (Fig. 1A). Furthermore, patients diagnosed outside their residential district were significantly more likely to experience a prolonged diagnostic odyssey than patients diagnosed within their district of residence (Fig. 1B). Of the patients who were diagnosed after 6 months from symptom onset, 34 patients (70.8%) were diagnosed outside of their residential region. Notably, patients who were older at symptom onset were significantly more likely to endure an extended di-

Table 2. Diagnostic odyssey of pediatric patients with rare diseases

Categories	No. (%)
Type of hospital initially visited	
Local hospital	38 (37.6)
Secondary or tertiary hospital	33 (32.7)
Emergency room	30 (29.7)
Time from initial hospital visit to final diagnosis	
<6 months	53 (52.5)
6 months to 1 year	16 (15.8)
≥1 year	32 (31.7)
Number of hospitals visited before diagnosis	
2–3	80 (79.2)
4–5	15 (14.9)
≥6	6 (5.9)
Medical costs paid before diagnosis (USD)	
<1,000	34 (33.7)
1,000–3,000	31 (30.7)
≥3,000	36 (35.6)
Medical costs paid after diagnosis (USD)	
<1,000	36 (35.6)
1,000–3,000	20 (19.8)
≥3,000	45 (44.6)
Residential area	
Seoul or Gyeonggi province	43 (42.6)
Others	58 (57.4)

USD, US dollar.

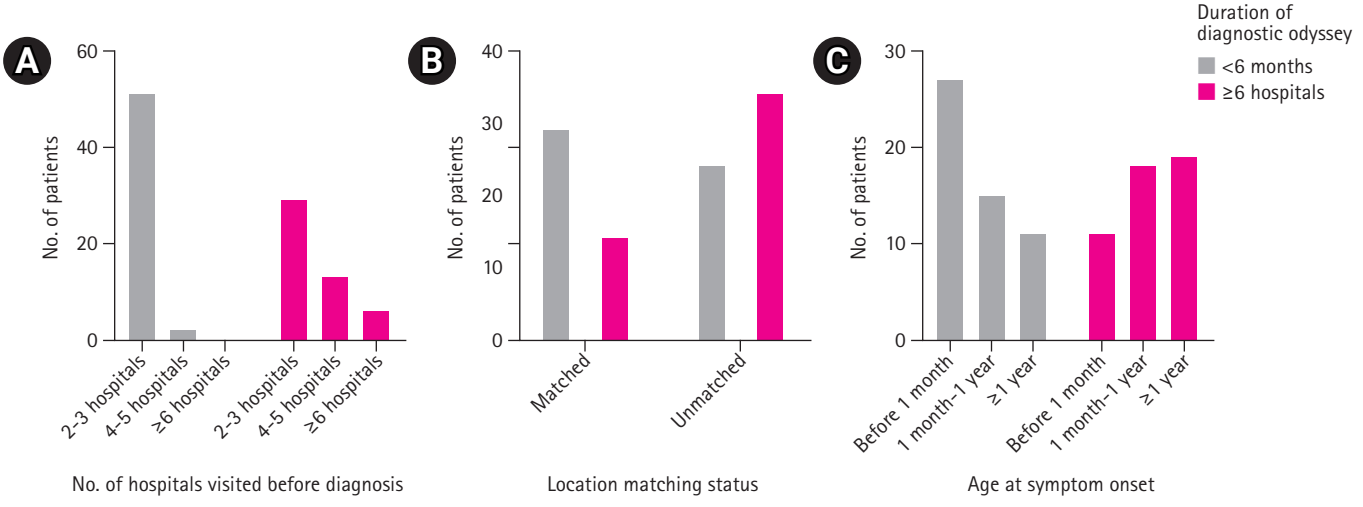

Fig. 1. Factors affecting the duration of the diagnostic odyssey. Patients were divided into two groups for analysis based on time to diagnosis following symptom onset: those with a diagnostic odyssey of less than 6 months and those with a duration of 6 months or more. (A) Patients who visited a greater number of hospitals (4–5 or more) were significantly more likely than patients who attended fewer hospitals to experience a diagnostic odyssey exceeding 6 months. (B) Patients were categorized based on whether the location of their diagnosing hospital matched their residential area. Those with alignment were classified as "matched," while those diagnosed outside their residential area were designated as "unmatched." Patients in the "unmatched" group were significantly more likely to experience a prolonged diagnostic odyssey. (C) Patients were classified according to the time of symptom onset: before 1 month, between 1 month and 1 year, and 1 year or more. Those with an earlier onset of symptoms were significantly more likely to report an extended diagnostic odyssey.

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agnostic journey (Fig. 1C). No other factors significantly affected the duration of the diagnostic odyssey in the study population.

Subsequently, we conducted a multivariate analysis to assess the combined impact of these significant factors on the time to diagnosis. The *P* values obtained from the logistic regression analysis for the three variables—number of hospitals visited, whether the residential district matched the diagnosed district, and age at symptom onset—were 0.006, 0.028, and 0.10, respectively.

3. Factors influencing satisfaction with medical care in families of pediatric patients with rare diseases

We surveyed families to gauge their satisfaction with the medical care currently being received. Based on their feedback, we divided families into two groups: those who found the care "not satisfactory or equivocal" and those who deemed it "satisfactory." Of all respondents, 31 (30.7%) reported being satisfied, while 70 (69.3%) expressed dissatisfaction or uncertainty about the medical care they were receiving. Our analysis, which employed chi-square tests to examine clinical factors associated with these patients and their families, identified two significant factors influencing satisfaction with current medical care. First, families who had faced higher medical costs before receiving a diagnosis reported a significantly greater degree of satisfaction with their current medical care. Specifically, within the group that had spent less than 1,000 USD, 28 respondents indicated that they were dissatisfied or equivocal, while six reported satisfaction. In contrast, among those who had spent at least 1,000 USD, 41 were dissatisfied or equivocal, while 25 expressed satisfaction (*P*=0.038) (Fig. 2A). Second, families who perceived moderate to severe limitations in cognitive functions displayed comparatively high satisfaction with the medical care received. Specifically, among caregivers of patients with no perceived limitations, 30 found the medical care unsatisfactory or equivocal, while seven expressed satisfaction. Among caregivers of those with moderate limitations, 26 respondents reported feeling unsatisfied or equivocal, while 22 were satisfied. Regarding caregivers of patients with severe limitations, three indicated feeling unsatisfied or equivocal, while two were reportedly satisfied with the care provided (*P*=0.033) (Fig. 2B).

Discussion

For the first time in Korea, we present a comprehensive characterization of patients with rare diseases and their families, as well as the factors impacting the duration of the diagnostic odyssey. The Korea Centers for Disease Control and Prevention has released statistics on rare diseases since 2019, reporting 52,069 cases in 2020 [16]. The enactment of the Rare Disease Control Act in 2016 was a key milestone for the management of rare diseases in Korea. Fol-

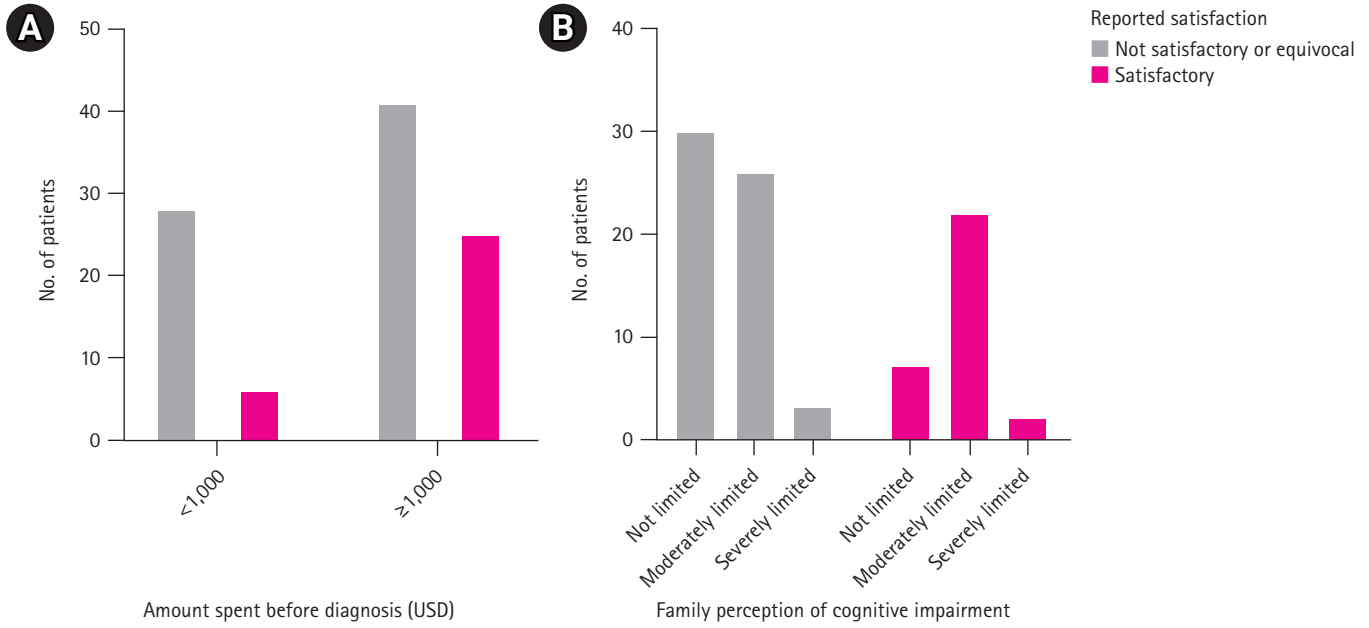

Fig. 2. Factors affecting satisfaction with medical care. Patients were divided into two groups for analysis: those with unsatisfactory or equivocal responses to their medical care and those with responses indicating satisfaction. (A) Families who incurred at least 1,000 US dollar (USD) of expenses were significantly more likely than families with lower costs to be satisfied with their medical care. (B) Patients were categorized based on their families' perceptions of their cognitive impairment. Relative to those perceiving no limitations, families indicating moderate or severe cognitive limitations were significantly more likely to be satisfied with the medical care provided.

lowing this, in 2017, the Korea Centers for Disease Control and Prevention introduced the first comprehensive plan for rare disease management. This strategy provided an overview of the current state of rare diseases, outlined strategies for problem management, emphasized the need to expand diagnostic capabilities, underscored the importance of treatment, advocated for better management support, and highlighted the need to strengthen research and development programs. Since 2001, the government has provided medical expense assistance to individuals registered under the Rare Disease Special Reimbursement Case program, designed specifically for patients with these conditions. However, challenges persist in the area of extremely rare diseases, which—even among rare conditions—have remarkably low prevalence rates. This creates gaps that are not covered as special reimbursement cases, often due to the lack of a diagnostic code or an unclear diagnosis name. Initiatives are also underway to support medical expenses, such as temporary aid for disaster-related medical costs and the establishment of a cap on out-of-pocket expenses. Despite these efforts to alleviate medical costs, the financial burden on patients and their families endures, particularly due to the costs associated with expensive unregistered tests and the extensive use of off-label drugs [17-19].

Despite concerted policy initiatives targeting rare diseases, it remains challenging for patients with rare diseases and their families to articulate the various obstacles they face, including unmet medical needs. This difficulty often stems from the isolation these individuals experience due to the rarity of their conditions, which can lead to a lack of social attention [20]. Consequently, interventions must be systematically and consistently applied, extending beyond medical treatment to include social support, psychosocial strategies, and policy improvements [21,22]. Our study, which provides a quantitative analysis of the time required to diagnose children affected by rare diseases, the factors impacting the duration of the diagnostic journey, and the level of satisfaction with the diagnostic process, should serve as a crucial foundation for the development of future rare disease policies in Korea.

The finding that over half of the families perceived the patients to be moderately or severely limited in both cognitive and motor functions (62.4% and 57.4%, respectively) underscores the need for multidisciplinary support. Additionally, the high rate of caregivers leaving their jobs to care for patients (53.5%) signals an urgent need for assistance not only for patients with rare diseases but also for the families caring for them. The call for comprehensive support, which includes both medical and psychosocial assistance for patients and their families, has been repeatedly highlighted in studies on rare diseases [23-26]. Our study meaningfully contributes to the global recognition of the need for multidisciplinary support for patients with these diseases and their families in Korea. In future research, a detailed analysis of caregivers' educational backgrounds, monthly incomes, and medical expenses before and after diagnosis would be instrumental in understanding the fundamental characteristics of this population. This information would provide valuable insights for future discussions of potential support policies.

Additionally, our study underscores the diversity of initial presenting symptoms and final diagnoses observed. The most common presenting symptom was developmental delay (27.7%), and the predominant final diagnosis was related to neurological conditions (49.5%). However, the spectrum of initial symptoms was broad, encompassing developmental regression, birth abnormalities, visual and hearing impairments, skin lesions, and intrauterine growth abnormalities. This variety speaks to the importance of a multidisciplinary team approach in the diagnosis of rare diseases. Consistent with numerous studies emphasizing the value of such teams in rare disease diagnosis [27-31], our findings regarding the varied presenting phenotypes at the onset of symptoms further reinforce the necessity of adopting a multidisciplinary team approach for diagnosing these conditions in Korea.

In this study, we clarified the characteristics of healthcare usage by patients with rare diseases and their families in Korea, along with the factors impacting the length of the diagnostic odyssey. Our study identified three variables associated with this duration: the number of hospitals visited, whether the districts of residence and diagnosis aligned, and the age at symptom onset. Given that an earlier onset of symptoms increases the likelihood of obtaining a confirmatory genomic diagnosis [32], early symptom onset will continue to play a key role in shortening the diagnostic odyssey, especially as genomic medicine advances. The number of hospitals visited and the correspondence between the residential and diagnostic districts are consistent with other studies [33,34], suggesting that individuals experiencing diagnostic delays are more likely to receive a diagnosis in a region outside of their area of residence. Consequently, they often must travel to visit hospitals or consult specialists—both within and beyond their local areas—and may experience an increased number of hospital visits. The impact of delayed referral is well recognized, as it not only affects the length of the diagnostic process but also the outcomes of many diseases, including rare conditions [35-37]. The findings from our study underscore the importance of establishing a networked referral system in Korea to reduce the diagnostic odyssey for patients with rare diseases. The awareness of primary care physicians about these diseases greatly affects the duration of the diagnostic odyssey for patients. Therefore, continuous efforts to provide education and information about rare diseases to the medical community are es-

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sential for improving patient outcomes [38,39].

Patient and family satisfaction with the medical care received was markedly associated with the medical expenses incurred. Contrary to conventional wisdom, those who faced higher annual medical costs reported significantly higher satisfaction with the quality of care received. This could stem from the increased access to medical services that often comes with higher healthcare spending [40,41]. However, to fully grasp this phenomenon, more research is needed. The present study did not explore the specifics of the patients' medical expenses beyond annual amounts.

Our study has several limitations that warrant attention. First, the analysis was conducted exclusively at a single tertiary center, with participation limited to patients and families who volunteered. The lack of both randomization and a multicenter enrollment strategy introduces the potential for selection bias, which necessitates caution when interpreting the study results. This bias may have contributed to the notably short diagnostic odyssey observed in our patient cohort, with over two-thirds (68.3%) experiencing a time to diagnosis of less than 1 year. Such a finding differs from reported diagnostic odysseys in research on rare diseases in Korea [12], emphasizing the need for broader, multicenter recruitment of patients and families to fully understand their characteristics. Second, our study was primarily focused on analyzing the quantitative characteristics of patients with rare diseases and their families. Although quantitative analysis provides valuable insights, it captures only a limited view of the complex dynamics of rare disease experiences. Third, our research was limited to the perceived cognitive and mobility functions of patients without corresponding objective assessments, which may have introduced bias in interpreting the results. In light of this, future research may benefit from adopting a mixed-methods approach [42] that includes qualitative aspects, offering a more nuanced understanding of the challenges faced by these patients and families.

Nonetheless, our study has several strengths. It is the first to comprehensively characterize patients with rare diseases and their caregivers, illuminating the factors influencing the length of the diagnostic journey. Our findings reveal the widespread severity of cognitive and motor impairments, as well as the high number of individuals who leave their jobs to provide patient care, underscoring the need for multifaceted socioeconomic support systems. Moreover, the wide range of initial symptoms underscores the importance of a multidisciplinary approach in diagnosis. Additionally, our research shows how disparities between a patient's place of residence and the location of diagnosis may prolong the diagnostic process, highlighting the critical need for an integrated referral system in Korea.

In conclusion, the comprehensive characterization of patients with rare diseases and their families in Korea, as well as an exploration of the factors influencing the length of the diagnostic odyssey, offers essential insights for the establishment of a support system tailored to the unique needs of this patient population and their families.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2024.00472.

Conflicts of interest

Jong Hee Chae is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: YJK. Data curation: JC, YSJ, JGY, SBL, and SYK. Formal analysis: JC and YSJ. Funding acquisition: JHC. Methodology: YJK. Project administration: JHC and YJK. Visualization: JC. Writing - original draft: JC and YSJ. Writing - review & editing: JC, JGY, SBL, SYK, JHC and YJK.

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References

1. Zurynski Y, Deverell M, Dalkeith T, Johnson S, Christodoulou J, Leonard H, et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. Orphanet J Rare Dis 2017;12:68.
2. Gahl WA, Mulvihill JJ, Toro C, Markello TC, Wise AL, Ramoni RB, et al. The NIH Undiagnosed Diseases Program and Network: applications to modern medicine. Mol Genet Metab 2016;117:393-400.

3. Baynam G, Pachter N, McKenzie F, Townshend S, Slee J, Kiraly-Borri C, et al. The rare and undiagnosed diseases diagnostic service: application of massively parallel sequencing in a statewide clinical service. Orphanet J Rare Dis 2016;11:77.
4. Dong D, Chung RY, Chan RH, Gong S, Xu RH. Why is misdiagnosis more likely among some people with rare diseases than others?: insights from a population-based cross-sectional study in China. Orphanet J Rare Dis 2020;15:307.
5. European Organisation for Rare Diseases. Survey of the delay in diagnosis for 8 rare diseases in Europe (EurordisCare2) [Internet]. Paris: EURORDIS; 2007 [cited 2024 May 11]. Available from: http://www.eurordis.org.
6. Molster C, Urwin D, Di Pietro L, Fookes M, Petrie D, van der Laan S, et al. Survey of healthcare experiences of Australian adults living with rare diseases. Orphanet J Rare Dis 2016;11:30.
7. Chinnery PF. Shortening the diagnostic odyssey: the impact of whole genome sequencing in the NHS. BMJ 2021;375:n2683.
8. Bordini BJ, Walsh RD, Basel D, Deshmukh T. Attaining diagnostic excellence: how the structure and function of a rare disease service contribute to ending the diagnostic odyssey. Med Clin North Am 2024;108:1-14.
9. Grady AC, Sid EWK. Multidisciplinary machine-assisted, genomic analysis and clinical approaches to shortening the rare diseases diagnostic odyssey [Internet]. Bethesda: National Center for Advancing Translational Sciences; 2024 [cited 2024 May 11]. Available from: https://ncats.nih.gov/research/research-activities/diagnostic-odyssey.
10. Baird PA, Anderson TW, Newcombe HB, Lowry RB. Genetic disorders in children and young adults: a population study. Am J Hum Genet 1988;42:677-93.
11. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis 2022;17:163.
12. Kim SY, Lim BC, Lee JS, Kim WJ, Kim H, Ko JM, et al. The Korean undiagnosed diseases program: lessons from a one-year pilot project. Orphanet J Rare Dis 2019;14:68.
13. Choi EK, Lee JW. Key findings from 2020 annual report on rare disease patients in Korea: incidence, mortality and medical service utilization. Public Health Wkly Rep 2022;15:2789-807.
14. Korea Disease Control and Prevention Agency. 2023 Designation of rare diseases for national management and publication of statistical yearbook [Internet]. Cheongju: Korea Disease Control and Prevention Agency; 2023 [cited 2024 May 11]. Available from: https://www.kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&act=view&list_no=723946.
15. Lee C, Lee J, Park S. Forecasting the urbanization dynamics in the Seoul metropolitan area using a long short-term memory-based model. Environ Plan B Urban Anal City Sci 2023;50:453-68.
16. Korea Centers for Disease Control and Prevention. Key findings of the statistical yearbook on rare disease patients. Cheongju: Korea Centers for Disease Control and Prevention; 2020.
17. Macnamara EF, D'Souza P; Undiagnosed Diseases Network, Tifft CJ. The undiagnosed diseases program: approach to diagnosis. Transl Sci Rare Dis 2020;4:179-88.
18. Fung A, Yue X, Wigle PR, Guo JJ. Off-label medication use in rare pediatric diseases in the United States. Intractable Rare Dis Res 2021;10:238-45.
19. Minghetti P, Lanati EP, Godfrey J, Sola-Morales O, Wong O, Selletti S. From off-label to repurposed drug in non-oncological rare diseases: definition and state of the art in selected EU countries. Med Access Point Care 2017;1:maapoc-0000016.
20. Currie G, Szabo J. Social isolation and exclusion: the parents' experience of caring for children with rare neurodevelopmental disorders. Int J Qual Stud Health Well-being 2020;15:1725362.
21. Witt S, Schuett K, Wiegand-Grefe S, Boettcher J, Quitmann J. Living with a rare disease: experiences and needs in pediatric patients and their parents. Orphanet J Rare Dis 2023;18:242.
22. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. BMC Fam Pract 2016;17:88.
23. Pelentsov LJ, Fielder AL, Esterman AJ. The supportive care needs of parents with a child with a rare disease: a qualitative descriptive study. J Pediatr Nurs 2016;31:e207-18.
24. Kenny T, Bogart K, Freedman A, Garthwaite C, Henley SM, Bolz-Johnson M, et al. The importance of psychological support for parents and caregivers of children with a rare disease at diagnosis. Rare Dis Orphan Drug J 2022;1:7.
25. Cardinali P, Migliorini L, Rania N. The caregiving experiences of fathers and mothers of children with rare diseases in Italy: challenges and social support perceptions. Front Psychol 2019;10:1780.
26. Kalbfell R, Wang W, Fishman S, Kerr AM, Sisk B. Burdens of disease and caregiver burden in complex vascular malformations. Pediatr Blood Cancer 2023;70:e30367.
27. Melo DG, de Paula PK, de Araujo Rodrigues S, da Silva de Avo LR, Germano CM, Demarzo MM. Genetics in primary health care and the National Policy on Comprehensive Care for People with Rare Diseases in Brazil: opportunities and challenges for professional education. J Community Genet 2015;6:231-40.
28. Kliegman RM, Ruggeri BE, Smith MM. The team-based ap-

 https://doi.org/10.26815/acn.2024.00472

proach to undiagnosed and rare diseases. Pediatr Clin North Am 2017;64:17-26.
29. Ormondroyd E, Mackley MP, Blair E, Craft J, Knight JC, Taylor J, et al. Insights from early experience of a Rare Disease Genomic Medicine Multidisciplinary Team: a qualitative study. Eur J Hum Genet 2017;25:680-6.
30. George RP, Winterberg PD, Garro R. Multidisciplinary and multidimensional approaches to transplantation in children with rare genetic kidney diseases. Pediatr Transplant 2023;27:e14567.
31. Splinter K, Adams DR, Bacino CA, Bellen HJ, Bernstein JA, Cheatle-Jarvela AM, et al. Effect of genetic diagnosis on patients with previously undiagnosed disease. N Engl J Med 2018;379:2131-9.
32. Wise AL, Manolio TA, Mensah GA, Peterson JF, Roden DM, Tamburro C, et al. Genomic medicine for undiagnosed diseases. Lancet 2019;394:533-40.
33. Martinez-Molina M, Argente-Escrig H, Polo MF, Hervas D, Frasquet M, Cortes V, et al. Early referral to an ALS center reduces several months the diagnostic delay: a multicenter-based study. Front Neurol 2020;11:604922.
34. Benito-Lozano J, Arias-Merino G, Gomez-Martinez M, Ancochea-Diaz A, Aparicio-Garcia A, Posada de la Paz M, et al. Diagnostic process in rare diseases: determinants associated with diagnostic delay. Int J Environ Res Public Health 2022;19:6456.
35. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G. Early referral and its impact on emergent first dialyses, health care costs, and outcome. Am J Kidney Dis 1998;32:278-83.
36. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. Am J Med 2011;124:1073-80.
37. Willmen T, Willmen L, Pankow A, Ronicke S, Gabriel H, Wagner AD. Rare diseases: why is a rapid referral to an expert center so important? BMC Health Serv Res 2023;23:904.
38. Vandeborne L, van Overbeeke E, Dooms M, De Beleyr B, Huys I. Information needs of physicians regarding the diagnosis of rare diseases: a questionnaire-based study in Belgium. Orphanet J Rare Dis 2019;14:99.
39. Walkowiak D, Domaradzki J. Are rare diseases overlooked by medical education: awareness of rare diseases among physicians in Poland: an explanatory study. Orphanet J Rare Dis 2021;16:400.
40. Fenton JJ, Jerant AF, Bertakis KD, Franks P. The cost of satisfaction: a national study of patient satisfaction, health care utilization, expenditures, and mortality. Arch Intern Med 2012;172:405-11.
41. Bogart K, Hemmesch A, Barnes E, Blissenbach T, Beisang A, Engel P, et al. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. Orphanet J Rare Dis 2022;17:196.
42. Creswell JW, Fetters MD, Ivankova NV. Designing a mixed methods study in primary care. Ann Fam Med 2004;2:7-12.