*Original Article*

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# Challenges associated with delayed definitive diagnosis among Japanese patients with specific intractable diseases: A cross-sectional study

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**SUMMARY** This study aimed to determine the challenges that cause a delay in the diagnosis of Japanese patients with specific intractable diseases by means of a survey. We conducted a questionnaire survey involving 424 patients with 12 specific intractable diseases. Pearson's chi-square test was used to examine the relationship between diagnostic delay and each factor. The reasons for the diagnostic delay were analyzed. Pearson's chi-square test showed statistically significant differences in the relationship between the period to definitive diagnosis and period between symptom onset and first hospital visit ($p = 0.002$), and the period when the patients suspected the disease ($p < 0.001$). Reasons for diagnostic delay of these patients were patients' time constraints, problem in access to medical institutions, hesitancy in seeking medical attention, and healthcare system issues. Early definitive diagnosis of intractable diseases was hindered by several important issues. The resolution of these issues will require combined societal efforts as well as improvements in the healthcare system. The study revealed the need for improving patients' awareness about their disease, enabling patients to be proactive towards achieving a definitive diagnosis, and making improvements in the healthcare system regarding early diagnosis and care of patients with intractable diseases.

***Keywords*** diagnostic delay, hospital visit, questionnaire

## 1. Introduction

Rare diseases, as indicated by the term, affect a small number of people; however, there are thousands of rare diseases. Therefore, the number of patients with rare diseases is quite high, and rare diseases are considered critical public health issues. Furthermore, the treatments for 94% of all rare diseases are insufficient, and many patients experience decades of uncertainty and challenges until they reach a definitive diagnosis (*1,2*). The difficulties in diagnosis and access to a specialist also frequently result in misdiagnosis and delayed diagnosis; therefore, it takes a long time for many patients to get a definitive diagnosis (*1,3*).

In addition, the prevalence and general awareness of individual rare diseases are low, resulting in many challenges regarding funds and access to clinical studies that demand international collaborative systems to overcome these barriers (*4*).

Rare diseases are also challenging for physicians to treat. Given the limited information regarding rare diseases, it is not uncommon for primary physicians, who are often the first health care providers with the opportunity to diagnose, to have little experience with rare diseases; hence, referral to a specialist is delayed. Such delays in diagnosis are attributed mainly to physicians lacking experience and information regarding rare diseases (*2*). Therefore, it is necessary to educate physicians about using online and other tools to quickly acquire information on rare diseases (*5*). Early definitive diagnosis is essential for patients with rare diseases because it can help guide them about methods and measures for controlling or slowing disease progression, even if no effective treatment exists (*6*). Furthermore, definitive diagnosis can improve the patient's quality of life (QOL) (*7*).

The European Union (EU) emphasized the importance of supporting "adequate education and training for all health professionals to make them aware of the existence of these diseases and resources available for their care" as actions against rare diseases in 2009 (*8*). The EU has also been the leader in building global data networks for rare diseases (*9*).

The vision of the International Rare Diseases

Research Consortium (IRDiRC) is to "enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within 1 year of coming to medical attention" by 2027 (*1*). Japan has been making parallel national and administrative efforts to build medical support networks for intractable diseases (*10*) and shorten the period to definitive diagnosis as much as possible. Such efforts define the "period to definitive diagnosis" as the "undiagnosed period", starting from when the patient first notices physical symptoms to when they seek medical attention. However, the undiagnosed period would be more accurate if it indicates the period from when the patient first notices the symptoms to when they visit a medical institution.

Previous research has identified two challenges affecting the period from symptom identification to the definitive diagnosis of intractable diseases (*11*). The first challenge is related to the high number of patients who wait to make a hospital visit after first noticing physical symptoms, whereas the second is related to the high number of patients from whom it takes a long time to reach a definitive diagnosis, despite the suspicion of the diagnosed disease for a very long time. Determining the reasons for these two challenges will aid in identifying the unmet needs and solutions that will help in shortening the undiagnosed period as well as the period to the definitive diagnosis.

Therefore, the present study addressed two research questions: *i*) why do patients wait to seek medical attention despite noticing physical symptoms, and *ii*) why does it take a long time for patients to reach a definitive diagnosis, despite suspecting the diagnosed disease for a very long time? This study aimed to address these research questions from the patient's perspective and identify the unmet needs.

## 2. Materials and Methods

We conducted an online questionnaire survey that included 488 participants with 12 specific intractable diseases recruited from a patient panel owned by Rakuten Insight, Inc., in February 2023. After excluding patients whose data could not be analyzed, 424 patients were finally included in the analysis. The data collection process in this study is shown in a flow chart (Figure 1). Furthermore, the various specific intractable diseases and the number of patients with each disease are presented in Table 1.

The questionnaire items consisted of basic sociodemographic data (age, sex, and location of residence), misdiagnosis experience, number of hospital visits until reaching a definitive diagnosis, time from the first medical consultation to reaching the current diagnosis, and period between first noticing the physical symptoms and the first medical consultation. These responses were selected from a list of options. The data from 424 patients were analyzed statistically using the following methods. A subanalysis of 133 patients – who took ≥ 6 months between first noticing physical symptoms and their first medical consultation – was performed to determine the reasons for delay in visiting a medical institution despite experiencing physical symptoms. Another subanalysis of 66 patients who suspected the diagnosed disease for ≥ 6 months was performed to explore the reasons why making a definitive diagnosis took a long time despite suspicions of the current diagnosis, which they answered by selecting responses from among several options. The questionnaire included a space for writing free responses to enable those who selected the "other" option to provide a specific reason. In addition, 141 patients, for whom it took ≥ 1 year to reach a definitive diagnosis, answered the following two questions: "What actions do you think you could have taken to shorten the period to a definitive diagnosis?" and "What kind of environmental or systemic changes do you think could have further shortened the period to definitive diagnosis?"

The IRDiRC's vision is to "Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within 1 year of coming to medical attention by 2027" (*1*). However, due to the lack of a standard definition for "delay to diagnosis", the

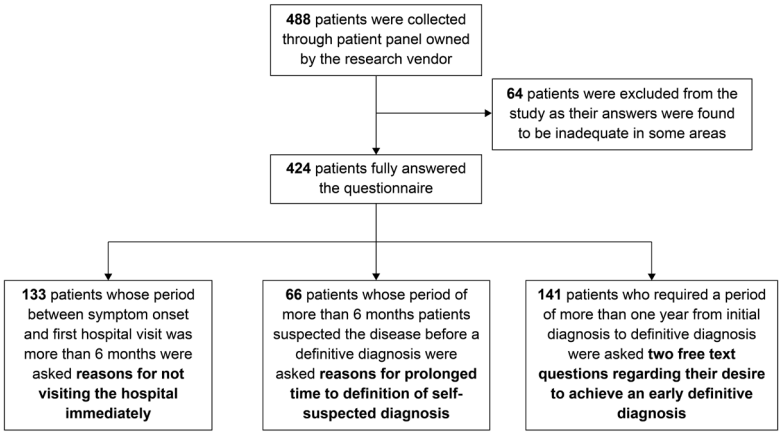


**Figure 1. Flow chart of data collection process.**

consortium guideline was used as the standard, defining diagnostic delay as ≥ 1 year from the first medical consultation to a definitive diagnosis.

### 2.1. Sample size

Sample size calculation was based on the following criteria: 5% margin of error, 95% confidence level, and 50% expected response rate. The sample size required for this study was at least 384 cases. The number of patients for each disease designated as intractable was used as a reference for the health administration reports published by the Ministry of Health, Labor and Welfare (*12*).

### 2.2. Analysis

IBM SPSS, ver28, (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) was used for statistical analysis.

The eligible data of 424 patients were included in the statistical analysis. Correlations between the period to definitive diagnosis (Diagnosis in 1 year and Diagnosis delay) and misdiagnosis experience, number of hospital visits, period between symptom onset and first hospital visit, and duration for which patients suspected the disease were analyzed using Pearson's chi-square test. Statistical significance was set at $p < 0.05$.

Thematic analysis was used for qualitative data (*13*). The analysis was performed using MAXQDA software 2022 (VERBI Software, 2021). We categorized the code into themes and clustered the themes. Themes, subthemes, and quotes are displayed in tabular form to facilitate the understanding of the phenomenon described.

The reason for not consulting a medical institution immediately, despite noticing physical symptoms, was selected by the respondents from among 12 options (multiple selections were allowed). Those who selected "other reasons" could write the specific reason in the free response form. The responses were interpreted and classified into the following themes: A) Factors associated with patients' access to healthcare facilities, B) time constraints for patients, C) patient-sided psychological factors, and D) other factors. Regarding the reason why it took a long period to reach a definitive diagnosis despite suspecting the diagnosed disease, patients were required to answer by selecting one or more from among seven options. Those who selected "other reasons" could also write the specific reason in the free response form. These options were classified into the following themes: A) Problems regarding medical facilities and healthcare systems, B) factors associated with one's actions, C) factors associated with situational changes, and D) other reasons.

### 2.3. Ethical approval

The data used in this study were consigned to Rakuten Insight, Inc. and obtained using the company's panel. All data obtained were fully anonymized before analysis. We had no access to the correspondence tables of anonymization or other information that could be used to identify the individuals. Therefore, this study used a completely anonymized questionnaire survey and was carried out in accordance with the method designated by the Research Ethics Review Committee, School of Health Innovation, Kanagawa University of Human Services. The same committee indicated that ethics approval was not required. The study notification number was SHI No. 59. The study's aims were explained to all the participants, who provided informed consent before participating in the survey.

## 3. Results

As shown in Table 1, this study focused on 12 diseases designated as specific intractable diseases in Japan, and analyzed the data of 424 patients.

The participant characteristics are shown in Table 2. Patients in their 60s accounted for the largest proportion of participants (30.7%), followed those aged 29–49 years (29.2%), 50–59 years (25.5%), > 69 years (13.0%), and < 29 years (1.7%). Furthermore, 27.1% of the patients experienced misdiagnosis. Notably, 8.5% of the patients took 6–12 months between first noticing physical symptoms and seeking medical attention for the first time, whereas 22.9% waited for > 1 year. Furthermore, 2.1% of the patients suspected having the diagnosed disease for 6–12 months, whereas 13.4% suspected having it for > 1 year. Notably, for 33.3% patients, the time from the first medical consultation to the definitive diagnosis was ≥ 1 year.

Next, Pearson's chi-square test was used to examine the correlations between the period to definitive diagnosis (diagnosis in 1 year and diagnosis delay) and misdiagnosis experience, number of hospital visits, period between symptom onset and first hospital visit, and duration for which the patients suspected the disease (Table 3). Chi-square test showed a statistically significant relationship between misdiagnosis and the period to definitive diagnosis ($p = 0.042$) (Table 3a). A relationship was also observed between misdiagnosis and delayed diagnosis. The correlation between the number of hospital visits until reaching a definitive diagnosis and the period to definitive diagnosis is shown in Table 3b, and a significant correlation was observed between both items ($p < 0.001$). A relationship was also observed between the number of hospital visits and the period to definitive diagnosis. There was a significant difference between the period to definitive diagnosis and the period between symptom onset and first hospital visit ($p = 0.002$) (Table 3c). Delayed definitive diagnosis occurred in 44.4% of patients who took 6–12 months between symptom onset and their first hospital visit, and in 44.3% of those who took > 1 year, clearly indicating that the

**Table 1. Patients with specified intractable diseases registered in this survey**

| Specified intractable disease | Number | Percentage (%) |
|---|---|---|
| Crohn's disease | 46 | 10.8 |
| Sjögren's syndrome | 45 | 10.6 |
| Polycystic kidney disease | 47 | 11.1 |
| IgA nephropathy | 50 | 11.8 |
| Systemic lupus erythematosus | 48 | 11.3 |
| Parkinson's disease | 30 | 7.1 |
| Idiopathic dilated cardiomyopathy | 28 | 6.6 |
| Multiple sclerosis/neuromyelitis optica | 28 | 6.6 |
| Spinocerebellar degeneration (excluding multiple system atrophy) | 19 | 4.5 |
| Idiopathic interstitial pneumonia | 40 | 9.4 |
| Eosinophilic sinusitis | 29 | 6.8 |
| Spinal muscular atrophy | 14 | 3.3 |

rate of delayed definitive diagnosis increased when the patients waited for > 6 months to seek medical help after the onset of symptoms. Furthermore, the patients who waited for a long time between first noticing physical symptoms and visiting a medical institution also experienced a long duration between the first medical consultation and definitive diagnosis. Furthermore, a significant difference was found between the period when patients suspected the disease and the period to definitive diagnosis ($p < 0.001$), as shown in Table 3d.

Furthermore, 55.6% of the patients who suspected the disease for 6–12 months and 66.7% who suspected the disease for > 1 year experienced delayed definitive diagnosis, indicating that patients who suspected the disease for ≥ 6 months experienced delayed definitive diagnosis. To explain the reason for these findings from the patient's perspective, we asked the patients who took ≥ 6 months to visit a medical institution despite noticing physical symptoms why they avoided visiting a medical institution, and their responses are presented in Table 4. The patients selected their answers from 12 options, and those who selected "other", described the specific reason in a free-response form. The most frequently cited reason was that they "decided to wait and see" (36.2%), followed by they "did not know which medical institution to visit" (15.1%), they thought "it was inconvenient to go to a medical institution" (9.3%), they "did not have time to visit a medical institution" (7.8%), they faced "difficulty making an appointment" (4.1%), they were "afraid of receiving a diagnosis" (4.1%), they were "afraid that a definitive diagnosis would affect their work or education" (3.8%), they had "no nearby medical institution" (3.5%), they were "afraid to visit a medical institution" (3.2%), and they had "financial concerns that prevented them from seeking medical help" (2.6%). In addition, 2.6% of the patients "did not consider it at all", and 7.8% provided "other reasons". These responses were interpreted and classified into four themes as follows: A) factors associated with patients' access to healthcare facilities, B) time constraints for patients, C) patient-sided psychological factors, and D) other factors, accounting for 32.0%, 44.0%, 11.1%, and 13.0% of the patients, respectively, as shown in Figure 2. Psychological factors seem to stem from problems such as the inability to continue working because the name of one's disease is revealed by visiting a medical institution, or hesitation to visit a medical institution because of prejudice from others.

**Table 2. Characteristics of the study sample**

| Characteristic | Number | Percentage (%) |
|---|---|---|
| Sex | | |
| Male | 256 | 60.4 |
| Female | 168 | 39.6 |
| Age | | |
| < 29 years | 7 | 1.7 |
| 29–49 years | 124 | 29.2 |
| 50–59 years | 108 | 25.5 |
| 60–69 years | 130 | 30.7 |
| > 69 years | 55 | 13.0 |
| Misdiagnosis experience | | |
| Yes | 115 | 27.1 |
| No | 309 | 72.9 |
| The period between symptom onset and first hospital visit | | |
| Immediately after symptom onset | 76 | 17.9 |
| < 1 month | 130 | 30.7 |
| 1–6 months | 85 | 20.0 |
| 6 months–1 year | 36 | 8.5 |
| > 1 year | 97 | 22.9 |
| The duration for which patients suspected the disease before a definitive diagnosis | | |
| Never doubted | 251 | 59.2 |
| < 1 months | 74 | 17.5 |
| 1–6 months | 33 | 7.8 |
| 6 months–1 year | 9 | 2.1 |
| > 1 year | 57 | 13.4 |
| The period from first hospital visit to definitive diagnosis | | |
| Diagnosis in 1 year | 283 | 66.7 |
| Diagnosis delay | 141 | 33.3 |

Table 5 presents the answers to the question regarding the reasons for the prolonged time to definitive diagnosis, despite having suspected the disease for ≥ 6 months. The most frequently cited reason was "extensive tests were conducted before the definitive diagnosis of the current medical condition, but the cause remained elusive, leading to a prolonged duration" (33.3%), followed by "prior misdiagnosis at previous healthcare facilities led to a belief in the incorrect diagnosis and subsequent delay in seeking specialized medical care" (17.2%), "lack of recommendation from physicians to seek specialized medical care contributed to the delay in visiting a specialized healthcare institution" (15.1%), "being busy and postponing their own visit to a specialized medical facility" (12.9%), and "limited access to specialized healthcare institutions in the residential area posed difficulties in seeking medical consultation" (8.6%). Furthermore, 2.2% of the patients responded that "the recent COVID-19 situation prevented proactive visits to hospitals for medical consultation" and 10.8% cited "other reasons". As shown in Figure 3, the themes A) problems regarding medical facilities and healthcare systems, B) factors associated with one's actions, C) factors associated with situational changes, and D) other reasons, accounted for 74.2%, 12.9%, 2.2% and 10.8%

**Table 3. Distribution of each independent variable and the definitive diagnosis period**

| | Study sample *n* (%) | Diagnosis in 1 year *n* (%) | Diagnosis delay *n* (%) | *p* | $\chi^2$ for trend |
|---|---|---|---|---|---|
| *3a. Distribution of misdiagnosis experience and the definitive diagnosis period* | | | | | |
| Misdiagnosis experience | | | | | |
| Total | 424 (100) | 283 (66.7) | 141 (33.3) | 0.042 | 4.122 |
| Yes | 115 | 68 (59.1) | 47 (40.9) | | |
| No | 309 | 215 (69.6) | 94 (30.4) | | |
| *3b. Distribution of the number of hospitals visited in the period before and after a definite diagnosis was made* | | | | | |
| Number of hospital visits | | | | | |
| Total | 424 (100) | 283 (66.7) | 141 (33.3) | < 0.001 | 22.569 |
| 1 visit | 156 | 114 (73.1) | 42 (26.9) | | |
| 2 visits | 164 | 118 (72.0) | 46 (28.0) | | |
| 3 visits | 63 | 35 (55.6) | 28 (44.4) | | |
| > 3 visits | 41 | 16 (39.0) | 25 (61.0) | | |
| *3c. Distribution of the period between symptom onset and first hospital visit and the definitive diagnosis period* | | | | | |
| Period between symptom onset and first hospital visit | | | | | |
| Total | 424 (100) | 283 (66.7) | 141 (33.3) | 0.002 | 16.864 |
| Immediately after symptom onset | 76 | 46 (60.5) | 30 (39.5) | | |
| < 1 month | 130 | 100 (76.9) | 30 (23.1) | | |
| 1–6 months | 85 | 63 (74.1) | 22 (25.9) | | |
| 6 months–1 year | 36 | 20 (55.6) | 16 (44.4) | | |
| > 1 year | 97 | 54 (55.7) | 43 (44.3) | | |
| *3d. Distribution of the period between suspicion of the disease and definitive diagnosis* | | | | | |
| The duration for which patients suspected the disease before a definitive diagnosis | | | | | |
| Total | 424 (100) | 283 (66.7) | 141 (33.3) | < 0.001 | 36.847 |
| Never doubted | 251 | 184 (73.3) | 67 (26.7) | | |
| < 1 month | 74 | 54 (73.0) | 20 (27.0) | | |
| 1–6 months | 33 | 22 (66.7) | 11 (33.3) | | |
| 6 months–1 year | 9 | 4 (44.4) | 5 (55.6) | | |
| > 1 year | 57 | 19 (33.3) | 38 (66.7) | | |

**Table 4. Reasons for delayed medical consultation despite perceiving physical symptoms**

| Option number | Description | Quantity of responses (%) | Clustered theme |
|---|---|---|---|
| 1 | I decided to wait and see. | 125 (36.2) | B |
| 2 | I did not know which medical institution to visit. | 52 (15.1) | A |
| 3 | It was inconvenient to go to a medical institution. | 32 (9.3) | A |
| 4 | I didn't have time to visit a medical institution. | 27 (7.8) | B |
| 5 | Lack of convenience in the medical institution (*e.g.*, difficulty in making appointments). | 14 (4.1) | A |
| 6 | I was afraid of receiving a diagnosis. | 14 (4.1) | C |
| 7 | I was afraid that a confirmed diagnosis would affect my work or education. | 13 (3.8) | C |
| 8 | There was no nearby medical institution. | 12 (3.5) | A |
| 9 | I was afraid to visit a medical institution. | 11 (3.2) | C |
| 10 | Financial concerns prevented me from seeking medical help. | 9 (2.6) | D |
| 11 | I didn't consider it at all. | 9 (2.6) | D |
| 12 | Other reasons. | 27 (7.8) | D |

of responses, respectively. These results suggested that the main reasons for delayed definitive diagnosis despite suspecting the disease for ≥ 6 months were associated with problems regarding medical facilities and healthcare systems.

Next, patients who took > 1 year to reach a definitive diagnosis were asked the following questions: "What actions do you think you could have taken to shorten the period to a definitive diagnosis?" and "What kind of environmental or systemic changes do you think could have further shortened the period to definitive diagnosis?" Notably, 141 patients who took > 1 year to reach the definitive diagnosis provided free-response answers that were qualitatively analyzed and classified

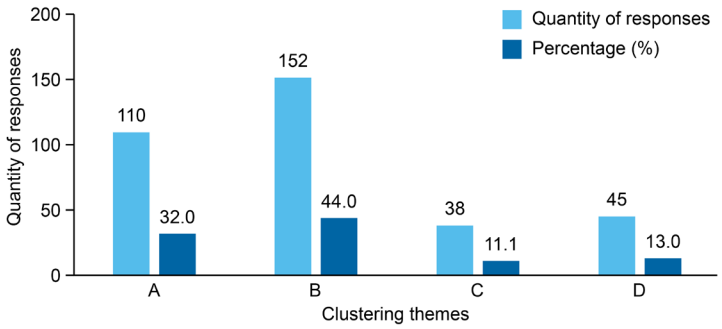


**Figure 2. Clustering themes of reasons for delayed medical consultation despite perceiving physical abnormalities. (A)** Factors related to patients' access to healthcare facilities; **(B)** Factors related to the time challenge of getting to the hospital; **(C)** Psychological factors; **(D)** Other factors.

**Table 5. Reasons for prolonged time to the definition of self-suspected diagnosis**

| Option Number | Description | Quantity of responses (%) | Clustered theme |
|---|---|---|---|
| 1 | Extensive tests were conducted before the definitive diagnosis with the current medical condition, but the cause remained elusive, leading to a prolonged duration. | 31 (33.3) | A |
| 2 | Prior misdiagnosis at previous healthcare facilities led to a belief in the incorrect diagnosis and subsequent delay in seeking specialized medical care. | 16 (17.2) | A |
| 3 | Lack of recommendation from physicians to seek specialized medical care contributed to the delay in visiting a specialized healthcare institution. | 14 (15.1) | A |
| 4 | Because I was busy and postponed my own visit to a specialized medical facility. | 12 (12.9) | B |
| 5 | Limited access to specialized healthcare institutions in the residential area posed difficulties in seeking medical consultation. | 8 (8.6) | A |
| 6 | The recent COVID-19 situation prevented proactive visits to hospitals for medical consultation. | 2 (2.2) | C |
| 7 | Other reasons. | 10 (10.8) | D |

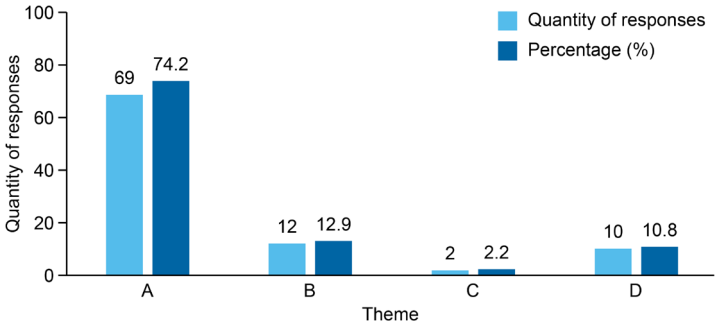


**Figure 3. Clustering themes of reasons for prolonged time to the definition of self-suspected diagnosis. (A)** Factors related to the medical facility or health care system; **(B)** Factors related to a decrease in one's willingness to visit a doctor; **(C)** Factors related to changes in circumstances; **(D)** Other factors.

into several themes and subthemes.

The free-response answers to the first question are presented in Table 6. The most frequently cited response was "having a strong interest in one's own symptoms" ($n$ = 75), followed by "cannot be improved by one's own actions alone" ($n$ = 48). Regarding "having a strong interest in one's own symptoms", the patients answered that having an interest in their symptoms would have led to them actively seeking medical attention, researching for information about their disease, and even seeking a second opinion. Regarding "cannot be improved by one's own actions alone", the patients expressed that attempts to change their behaviors would not have accelerated the process of reaching a diagnosis; however, improved efficiency of the healthcare system and access to health screening data might have shortened their time to diagnosis. Relationship of trust with the physician was another factor that patients indicated as a condition for effectively reaching an early diagnosis. In addition, topics related to the COVID-19 pandemic were also mentioned.

Next, the free responses to the second question are presented in Table 7. The most frequently cited response was "better systems for early diagnosis" ($n$ = 105), where the respondents mentioned the importance of correcting regional disparities in terms of effective use of health

**Table 6. Themes from the free text comments regarding what actions the patients themselves could have taken to shorten the time to a definitive diagnosis**

| Theme | Subthemes | Number | Quotes |
|---|---|---|---|
| Having a strong interest in one's own symptoms | Arranging work schedules to decide on early medical consultation | 75 | *I was unable due to my work engagements. (Respondent 187)*<br>*I didn't go to a hospital even though my symptoms were getting worse. I wonder whether my condition would have changed if I had visited a hospital earlier, so I believe it's necessary to take early action. (Respondent 70)* |
| | Active use of second opinion doctors | | *I should've taken advantage of a second opinion more actively. (Respondent 404)* |
| | Independently researching on the disease | | *I should've been more interested in my own body and told someone about it, even about small things like symptoms. (Respondent 304)*<br>*I should have contacted the appropriate institution to get access to a medical consultation that would have allowed me to find the appropriate medical facility. (Respondent 332)* |
| Cannot be improved by one's own actions alone | Building a healthcare system that allows early diagnosis | 48 | *It would accelerate the process if we could go directly to a specialized institution, such as a national hospital, without a referral. (Respondent 155)* |
| | Effective and active use of health screening data | | *There was a long watch-and-wait period after getting the test results. While waiting for the next health checkup, I should have visited other medical institutions, or been re-tested. (Respondent 268)*<br>*There was nothing I could do about it. It's a problem of cooperation between medical institutions (or lack thereof). (Respondent 38)* |
| Environmental changes | Effects of the COVID-19 pandemic | 1 | *At first, I consulted my family doctor and had the family doctor write a referral to a university hospital. However, it was summer, and I didn't have the energy to put a mask on and go out, and it would have taken a long time to walk, so I could not go out.*<br>*It was very tough walking, dragging my feet. (Respondent 101)* |
| Building a relationship of trust with the physician | Building a relationship of trust with the physician | 3 | *I should have built a relationship of trust with the physician. (Respondent 298)* |
| I do not know | | 14 | |

**Table 7. Themes from free text comments regarding requests for improvements in the medical environment and system**

| Theme | Subthemes | Number | Quotes |
|---|---|---|---|
| Better systems for early diagnosis | Effective use of health screening data | 105 | *would be referred to a doctor with knowledge and experience, not just someone who reads the health screening results. (Respondent 268)* |
| | Support to take advantage of a second opinion | | *It's nice that we have this system to seek a second opinion, but how useful is it really?? When you don't know what disease you have, it is hard to find a new hospital, so active referral by the physician would be helpful. (Respondent 482)* |
| | Definitive diagnosis by the family physician | | *The system should have the family physician make a definitive diagnosis before they refer the patient to a specialized hospital (in my case, a university hospital). That is, it would be great if the patient can find out that they have a specific intractable disease as early as possible. (Respondent 69)* |
| | Increased accuracy of tests | | *I thought it would accelerate the process to definitive diagnosis if all the tests could be done at once. (Respondent 356)*<br>*It would be ideal if we weren't sent to specialized departments, but to a physician or department who can make a multifaceted, overall assessment so that we are not left with the diagnosis "reason unknown". (Respondent 39)* |
| | Medical fee coverage support | | *My disease is not severe, so I would not get financial assistance even if my diagnosis is confirmed. The tests that led to my definitive diagnosis did cost a lot of money, though. I'm sure it depends on the disease, but financial support to get the diagnosis may increase the number of people who get the definitive diagnosis.(Respondent 148)* |
| | Accessibility of hospital consultations | | *It is so hard to get an appointment. I get completely exhausted while waiting at the hospital. It might have made a difference somewhat if these problems were solved. (Respondent 408)*<br>*hospitals opening on Saturdays and Sundays. (Respondent 37)* |
| | Correcting regional disparities in medical service accessibility | | *I think it's a problem that there are no specialists in rural areas. (Respondent 77)* |
| Having a strong interest in one's own symptoms | Strong motive to come to terms with one's illness | 3 | *It was my own problem, so it's not so much a matter of the environment or systems, but a problem of individual mentalities. I mean, most people won't imagine getting such a disease. (Respondent 70)* |
| Building a relationship of trust with the physician | Building a relationship of trust with the physician | 1 | *relationship of trust with the physician. (Respondent 298)* |
| I do not know | | 32 | |

screening data, supporting second opinions, definitive diagnosis by the family physician, increased accuracy of tests, medical fee coverage, and accessibility to hospital visits.

Regarding "Having a strong interest in one's own symptoms", the respondents indicated the importance of having a strong motive to come to terms with one's illness. The theme of "building a relationship of trust with the physician" also emerged.

## 4. Discussion

As shown in Table 3c, many patients who waited a long time between the first onset of symptoms and the first medical consultation took a long time to reach a definitive diagnosis, even after seeking medical attention. To determine the reasons for this phenomenon, we surveyed the reasons why the patients did not immediately visit a hospital (Figure 2); the reasons were mainly associated with time constraints for patients and access to medical institutions in most cases (76%). These patients seemed to either not think too deeply that they might be affected by an intractable disease or were aware that it was possible but did not think too much about it. Therefore, boosting incentives for these patients to seek medical attention, such as providing information about diseases to patients, would increase their chances of getting an early diagnosis. Regarding patients' psychological factors, which accounted for 11.1% of participants, it seemed unlikely that mere attempts to boost their motivation would lead to an early diagnosis because they experienced anxiety about visiting medical institutions. Many patients who hesitate to seek medical care are concerned about the potential consequences of a definitive diagnosis, such as becoming unable to continue their current employment, losing their source of income, or facing prejudice from their workplace or the communities they are involved in. Therefore, we need to not only to address medical issues but also foster a broader societal transformation that embraces patients with intractable diseases and makes them feel included in society.

Regarding the reasons it took a long time to reach a definitive diagnosis despite the patient suspecting the disease for > 6 months, problems regarding medical facilities and healthcare systems were the most frequent reasons (Figure 3). Patients seemed to have a strong desire for improvements in the healthcare system. Furthermore, when the patients who took > 1 year to reach a definitive diagnosis were asked, "what actions do you think you could have taken to shorten the period to definitive diagnosis?", the most frequently cited reason was "having a strong interest in one's own symptoms". Patients' research about the disease and actively seeking a second opinion were also positive actions to avoid delayed definitive diagnosis. Notably, patients mentioned that the presence of a physician they trusted might shorten the time to definitive diagnosis and time to the introduction of appropriate care; however, this was limited to a minority. Our previous research showed that patients who experienced delayed diagnosis scored low on parameters of trust in their physician (*11*). This topic needs further investigation.

Our results suggested the importance of changes to medical facilities and systems and ways to ensure the patients are motivated to seek medical attention to shorten the period to the definitive diagnosis of intractable diseases. In such cases, motivation should not only involve encouraging them to visit a medical institution but also involve creating a social environment that is accepting of patients with intractable diseases and where patients and their families can obtain the latest information.

Researchers studying rare diseases are also obtaining a broad spectrum of precise associated data. Patients with rare diseases are geographically dispersed, and it is difficult to aggregate information into a single database. However, recent efforts are made using social media platforms to help find patients with similar intractable health problems and also clinicians with expertise in rare diseases. It is aimed to promote sharing of information on symptoms, treatments, side effects, other diseases and activities, and other various data types beyond those typically captured in a clinical setting or patient registry (*14*). In addition, Klein *et al.* (*15*) recently used Twitter to receive the data on rare health-related problems reported by patients and found it useful for collecting patient-centered information that can be used in future epidemiological analyses.

Yamaguchi *et al*. (*16*) are exploring how data from the medical histories of patients with rare diseases posted on social media can capture patients' perspectives on their health status and assist in speeding up the timeline to diagnosis and treatment. Such an initiative would be useful to researchers and also could motivate undiagnosed patients worldwide to seek medical attention.

The present study identified two important aspects: Firstly, patients who spend a long time until their initial consultation tend to experience a prolonged duration from the initial consultation to a definitive diagnosis, and we have identified the reasons behind this phenomenon. Secondly, there is a prevalent trend among patients who have harbored suspicions about their own illness for an extended period but still experience delays in receiving a definitive diagnosis. We identified the factors contributing to this problem.

However, this study also has some limitations. First, the data was collected through a questionnaire survey aimed at collecting patient input from their perspective. To gain further in-depth patient insight, conducting a survey through interviews is also necessary. In particular, interviews could have provided deeper insights regarding the reasons why the patients were reluctant to visit

healthcare facilities. However, we aimed to obtain the largest possible sample size and broad range of information. Therefore, we believe that the questionnaire-based approach used in our study was appropriate for this purpose. In future, an in-depth investigation regarding the reasons for combining the interviews with surveys may become necessary. Furthermore, future studies should also conduct surveys of physicians to gain a better understanding of challenges experienced in healthcare facilities and identify other unmet needs that lead to delayed diagnosis of patients with intractable diseases.

This study has raised several important issues regarding early definitive diagnosis of intractable diseases. Initiatives by organizations such as IRDiRC and governmental organizations aim to shorten the duration between when patients visit a medical institution and when they receive a definitive diagnosis. However, we believe that the term "undiagnosed period" should refer to the duration from when patients first notice bodily changes to the point at which they receive a definitive diagnosis. In this study, it was observed that many patients who did not immediately seek medical help upon noticing bodily changes and those who spent a long duration until seeking care also experienced diagnostic delay. Moreover, patients who harbored suspicions about their own illness for an extended period also experienced diagnostic delay. In this study, we have elucidated the underlying factors behind why these patients experience delays in receiving a definitive diagnosis.

To fundamentally address these issues, it is crucial to not only focus on improving the current healthcare system, which the government is currently undertaking, but also to raise awareness among patients about their conditions, promote proactive efforts toward obtaining a definitive diagnosis, and foster a societal transformation that embraces patient with intractable diseases and addresses these medical challenges.

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