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Research paper

Anxiety level and clinical course of patients with sickle cell disease during the COVID-19 outbreak

O. Tezol a,*, S. Unal b

a Department of Pediatrics, Mersin University, Faculty of Medicine, Mersin, Turkey
b Department of Pediatrics, Division of Pediatric Hematology, Mersin University Faculty of Medicine, Mersin, Turkey

1. Introduction

Coronaviruses (CoV) are a large family of viruses that usually cause respiratory tract illnesses such as the self-limiting common cold or more serious infections called Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). SARS-CoV emerged as a previously unknown virus in 2003 as the first global health emergency of the 21st century. About 10 years later, MERS-CoV from the coronavirus family, which had not previously been demonstrated in humans or animals, was first identified in humans. On December 31 2019, the World Health Organization China Country Office reported pneumonia cases of unknown etiology in Wuhan, Hubei province. On 7 January 2020, the causative agent was identified as a new coronavirus (2019-nCoV) that had not previously been detected in humans. Then the name “2019-nCoV” was accepted as “SARS-CoV-2”, and the name of disease was accepted as COVID-19. It subsequently spread very rapidly around the world. The first confirmed COVID-19 case in Turkey was announced in the early hours of March 11, 2020 [1–3].

The common symptoms of COVID-19 are fever, cough, shortness of breath, and dyspnea. In more serious cases, pneumonia, severe acute respiratory infection, kidney failure, or even death may develop [2,3]. In addition to the risk of infectious pneumonia and death, the COVID-19 pandemic prompted negative psychological impacts to communities and adversely affected psychosocial stability and mental resilience. Social distancing, quarantine, isolation, commuting, and schooling restriction practices, fear of becoming infected, suffering severe infection, losing loved ones, and news on COVID-19 deaths have caused psychological distress [4–6]. Negative psychological outcomes such as depression, anxiety, stress, and fear were reported during the COVID-19 outbreak [6–9]. Liang et al. emphasized that...
infectious diseases such as COVID-19 may have an immense influence on youth mental health [10]. In the pandemic circumstances, patients with chronic illness received particular attention, because the presence of concomitant systemic diseases (especially secondary immunosuppressive conditions) was reported to increase the risk of severity and mortality of COVID-19. Moreover, COVID-19 may increase the risk of complications of chronic illnesses [11]. In addition to physical health problems, patients with chronic diseases may experience psychological problems such as anxiety, emotional disturbance, and anger during the outbreak [12].

The final impacts of COVID-19 have not yet been defined because the process of active infection, transmission, testing, treatment, recovery, and mortality has still not been terminated. However, it has already been defined that an outbreak creates anxiety [13–16]. From this point of view, COVID-19-related anxiety has been reviewed by Fardin, and psychological health was suggested to be adversely affected in the general population, especially in vulnerable groups, during the COVID-19 outbreak [5]. Due to quarantine, restrictions, and mental stress, anxiety may occur among patients with chronic diseases as a vulnerable group. Patients with chronic illness may suffer from anxiety because of the traumatic course of severe COVID-19, fear of death and the experience of witnessing others dying [12].

Sickle cell disease (SCD) is a monogenic disorder characterized by the production of sickle hemoglobin and patients undergo hemolytic anemia, vaso-occlusive and sequestration crises, and multiple complications. An adverse psychosocial impact is one of the complications of SCD. Quality of life, psychosocial well-being, daily personal and social life, and affectivity may be negatively affected in SCD patients [17–19]. In Turkey, the total number of patients with SCD is approximately 10 000; the frequency of sickle hemoglobin is 0.03%. SCD is prevalent in the Çukurova region of southern Turkey where Mersin is located, which has a 13.6% incidence of the sickle cell trait (Hb AS) [20]. SCD patients with a higher frequency of painful episodes were reported to have increased state anxiety levels: more anxious patients were reported to have more pain, pain-related distress, and higher admission rates for pain [21,22]. SCD patients may have already accepted they are vulnerable to anxiety. However, no study on the anxiety status of SCD patients facing the COVID-19 outbreak has yet been conducted. Therefore, we evaluated the outbreak-related experiences and the state and trait anxiety levels of adolescent and young adult patients with SCD with the following objectives: (1) to detect the frequency of anxiety during the COVID-19 outbreak by measuring the state anxiety level; (2) to determine whether there is any increase in anxiety by comparing state and trait anxiety levels; (3) to document COVID-19-related experiences and clinical course during the outbreak; and (4) to analyze correlations between the COVID-19 experiences and anxiety levels and painful episodes.

2. Methods

A cross-sectional study was conducted on the state and trait anxiety levels of adolescents and young adults with homozygous SCD. Forty-seven sickle cell anemia (SCA) patients monitored in the Pediatric Hematology department, aged between 14 and 24 years, using WhatsApp Messenger on their smartphones were included. The inclusion criteria were as follows: (1) at least secondary school graduates; (2) no history of psychiatric and/or cognitive disorder; (3) no history of chronic conditions (other than those secondary to SCD); (4) no history of marriage and/or having a child; (5) living with their family in Mersin; and (6) willingness to participate in the study. The study was carried out from May 10 to May 20, 2020. The local ethics committee approved the study.

Forty-seven patients were called and the purpose and procedure of the study were described in the phone call. Then an instrument and State-Trait Anxiety Inventory forms in Word format were sent via WhatsApp from the first author’s smartphone to the patients’ smartphones. The patients completed the instrument and the State-Trait Anxiety Inventory, and returned the responses with WhatsApp within the same day.

The descriptive instrument, designed by co-authors, consisted of 11 questions. The first five questions described negative COVID-19-related experiences and they were written using the Coronavirus Anxiety Scale as a reference [23]. The first five questions examined experiences of dizziness, sleep disturbance, tonic immobility, appetite loss, nausea and abdominal distress over the last 2 months, and the responses were designed as “never,” “sometimes,” “frequently,” “almost always.” Questions 6–10 examined episodes of pain, analgesic use, and need for medical care histories over the last 2 months. The 11th question was an open-ended question that inquired about the most preferred relaxing activity during the COVID-19 outbreak. The first coronavirus case was confirmed on March 10, 2020 in Turkey, so the instrument questions were designed to exam data between the dates of March 10 and May 10, 2020.

The State-Trait Anxiety Inventory (STAI) is commonly used to measure via self-reporting, the trait and state anxiety, and consists of 20 items for assessing trait anxiety and 20 for state anxiety. Both scales have anxiety-absent and anxiety-present questions. All items are rated on a 4-point scale for S-anxiety: (1) not at all, (2) somewhat, (3) moderately so, (4) very much so; for T-anxiety: (1) almost never, (2) sometimes, (3) often, (4) almost always. The scores range from 20 to 80, with higher scores correlating with greater anxiety. State anxiety can be defined as a transient momentary emotional status that results from situational stress, and a cut-off point of 39–40 can detect clinically significant symptoms. Trait anxiety represents a predisposition to react with anxiety in stressful situations [24,25]. STAI has good support for its validity and reliability in the Turkish population above 14 years of age [26].

A painful crisis or blood/exchange transfusion features requiring hospitalization on the dates of March 10 to May 10 2020 and March 10 to May 10, 2019 were collected as seasonally adjusted clinical data by reviewing medical records. “History of travel, contact, and symptoms suggestive of COVID-19 were also reviewed.

2.1. Statistical analysis

The data were analyzed using the SPSS 21 statistics program. Number and percentage values are given for the categorical variables. The Shapiro–Wilk test and histograms were used to test for normality. Adolescents’ and young adults’ anxiety scores were compared using the Student t-test. The Wilcoxon test was used to compare state and trait anxiety scores. The correlations between the number of COVID-19- and SCA-related experiences were analyzed using the Spearman rank correlation. Clinical data for the same period of two sequential years were compared with the Wilcoxon test or the McNemar test. The statistical significance level was set as P < 0.05.

3. Results

All of the 47 patients who met the inclusion criteria and received a phone call and WhatsApp message participated in the study. The median (range) age of the patients was 18.2 (14–24) years, and 70.2% of the patients were male. None of the patients had a history of travel or contact with person(s) infected with
SARS-CoV-2. During the study period, three patients had fever and/or respiratory symptoms and showed negative results for SARS-CoV-2 on the nucleic acid test.

Symptoms of dizziness, sleep disturbance, tonic immobility, appetite loss, nausea and abdominal distress were experienced by patients in varying percentages, and 42.6% of the patients had painful episode(s) with a median number of one (to four) episode on pandemic days. COVID-19- and SCA-related experiences are shown in Table 1.

According to the first five questions of the instrument, 16 (34%) patients had no negative COVID-19 experience while 15 (31.9%) patients had one negative COVID-19 experience, eight (17%) patients had two, five (10.6%) patients had three, and three (6.4%) patients had four negative COVID-19 experiences. The median (range) number of COVID-19 experiences in the study group was one (zero to four).

The median (range) values of the state and trait anxiety scores were 34 (21–60) and 39 (23–59), respectively; the difference in the state and trait anxiety scores was significant ($P < 0.001$). The state and trait anxiety scores were strongly correlated ($P = 0.600, P < 0.001$) and did not vary by gender or age ($P > 0.05$).

Adolescents (14–18 years of age, $n = 23$) and young adults (19–24 years of age, $n = 24$) had similar state anxiety scores ($36.2 \pm 11.0$ vs $33.8 \pm 9.7, P = 0.443$) and similar trait anxiety scores ($42.3 \pm 10.2$ vs $39.5 \pm 9.6, P = 0.340$). There were 16 patients (34%) with a state anxiety score above 39.

Correlation analysis showed that the number of COVID-19 experiences was correlated with the state anxiety score, the trait anxiety score, and the number of painful episodes ($P = 0.552, P < 0.001$; $P = 0.529, P < 0.001$; $p = 0.448, P = 0.002$, respectively). The state anxiety score and the number of painful episodes were moderately correlated ($p = 0.402, P = 0.005$) while the state anxiety score and the number of analgesic uses were not correlated ($p = 0.276, P = 0.060$). The trait anxiety score and the number of painful episodes were weakly correlated ($p = 0.357, P = 0.014$) while the trait anxiety score and the number of analgesic uses were not correlated ($p = 0.261, P = 0.076$).

Comparisons of clinical features requiring hospitalization for the same period of two sequential years are shown in Table 2. Vaso-occlusive crisis and blood/exchange transfusion features were similar on the two dates: March 10 to May 10, 2020, and March 10 to May 10, 2019.

### Table 1
Descriptive instrument data: COVID-19-related [23] and SCA-related experiences over the last 2 months.

| Question                                                                 | Never          | Sometimes      | Frequently     | Almost always |
|--------------------------------------------------------------------------|----------------|----------------|----------------|---------------|
| I felt dizzy or faint                                                   | 33 (70.2)      | 10 (21.2)      | 2 (4.3)        | 2 (4.3)       |
| I had trouble falling asleep or staying asleep                          | 30 (63.8)      | 7 (14.9)       | 4 (8.5)        | 6 (12.8)      |
| I felt frozen and I was in a quandary                                    | 31 (65.9)      | 13 (27.7)      | 3 (6.4)        | –             |
| I lost my appetite and interest in eating                               | 43 (91.5)      | 3 (6.4)        | 1 (2.1)        | –             |
| I felt nauseous and had stomach problems                                | 40 (85.1)      | 7 (14.9)       | –              | –             |

**Over the last 2 months**

| Experience                                                              | No             | Yes            |
|-------------------------------------------------------------------------|----------------|----------------|
| I have had painful episode(s)                                           | 27 (57.4)      | 20 (42.6)      |
| I have used analgesics drugs                                            | 18 (38.3)      | 29 (61.7)      |
| I have increased use of analgesic drug                                  | 31 (65.9)      | Increased by < 25%: 13 (27.7) Increased by 25–75%: 1 (2.1) Increased by > 75%: 2 (4.3) |
| Although I had complaints, I refrained from going to the hospital       | 33 (70.2)      | 14 (29.8)      |
| I needed medical care because I did not feel well and healthy           | 32 (68.1)      | 15 (31.9)      |
| The most frequent activity I did to feel good and healthy was           |                 |                |
| Doing sports/exercise                                                  | 9 (19.1)       |                |
| Listening to music                                                     | 8 (17.0)       |                |
| Watching a TV show/movie                                               | 7 (14.9)       |                |
| Video gaming, social media use                                          | 6 (12.8)       |                |
| Reading a book                                                         | 6 (12.8)       |                |
| Studying                                                                | 4 (8.5)        |                |
| Talking on the phone                                                   | 3 (6.4)        |                |
| Going out on the balcony                                               | 2 (4.3)        |                |
| Photography                                                            | 1 (2.1)        |                |
| Playing a guitar                                                       | 1 (2.1)        |                |

Data are number (percentage); SCA: sickle cell anemia.
a 1 (1–4).
b 2 (1–15).
c 1 (1–4).
d 1 (1–3); median (range) number of SCA-related experiences.

### Table 2
Comparisons of clinical features requiring hospitalization for the same period of two sequential years.

| Feature                        | March 10–May 10, 2020 | March 10–May 10, 2019 | $P$ |
|--------------------------------|------------------------|------------------------|-----|
| Number of experiences per patient | 0 (0–3)                | 0 (0–3)                | 0.371* |
| Painful symptoms                | 0 (0–3)                | 0 (0–2)                | 0.454* |
| Blood/exchange transfusion      | 0 (0–3)                | 0 (0–2)                | 0.454* |
| Number of patients who          |                        |                        |     |
| Had vaso-occlusive crisis       | 13/47 (27.7)           | 8/47 (17.0)            | 0.267* |
| Needed blood/exchange transfusion| 7/47 (14.5)            | 4/47 (8.5)             | 0.453* |

* Wilcoxon signed rank test; data are median (range).

* McNemar test; data are number (percentage).
4. Discussion

COVID-19 has caused a global health crisis and resulted in a pandemic. The spread of SARS-CoV-2 around the world has impacted human physical and psychological health [27]. Patients with chronic disease may experience increased anxiety and a preexisting medical problem increases risk for adverse psycho-social outcomes during the COVID-19 outbreak [28]. We speculate that SCA patients may also be vulnerable to increased anxiety in the current pandemic. Starting from this point of view, the main objectives of this study were detecting frequency of anxiety during the COVID-19 outbreak by measuring patients’ state anxiety level and determining whether anxiety had increased by comparing patients’ state and trait anxiety levels. With respect to the first goal, we found that 34% of the patients had state anxiety with a state anxiety score above 39. This frequency is similar to the general population, in a systematic review and meta-analysis, the prevalence of anxiety was reported to be 31.9% (95% confidence interval, 27.5–36.7) among the general population during the COVID-19 pandemic [29]. As regards the second purpose, contrary to our predictions, comparison of the STAI scores revealed that the median state anxiety score was significantly lower than the median trait anxiety score. Actually, this result was not surprising because both median state and trait anxiety scores were below the cut-off scores indicating significant clinical symptoms [25,30]. This result did not indicate that states of calmness, confidence, and security were poorer in general than in the pandemic period.

In the present study, one out of every three patients had a state anxiety score indicating clinically significant symptoms. Also, one out of every three patients said that he/she needed needed medical care because of not feeling well. Two out of every three patients had at least one negative COVID-19 experience. Dizziness, sleep disturbance, tonic immobility, appetite loss, nausea, and abdominal distress are symptoms associated with clinically elevated anxiety, and these symptoms were the items of Coronavirus Anxiety Scale developed by Lee [23]. We took this scale as a reference but we did not use it to screen patients because it had not been validated in a Turkish population. With regard to the third and fourth objectives of this study, the results showed that every symptom was experienced by patients at varying percentages on pandemic days. The number of negative COVID-19 experiences was correlated with the number of painful episodes during the outbreak and the anxiety scores. Consequently, mental health care is recommended for young SCA patients in pandemic times because anxiety and painful episodes decrease if pandemic-related symptoms are relieved. We believe that the descriptive and correlation findings are the main strengths of this study because it is the first report in the literature on COVID-19-related anxiety in young SCA patients.

Living in urban areas, living with parents, and not having a relative or an acquaintance infected with COVID-19 were reported to be protective factors for anxiety, and gender was not found to be associated with the level of anxiety symptoms in a young Chinese study [6]. Mersin is an urban area, the patients were living with family, and none of the family members had tested positive for SARS-CoV-2 in this study. Hypothetically these characteristics may have been associated with nonsignificant state anxiety. SCA did not appear in the media or in public service ads as a risky chronic condition during the COVID-19 outbreak in Turkey. Elderliness and hypertension, diabetes, cardiovascular diseases, and chronic lung diseases were frequently announced as high-risk conditions [3]. This may have provided our young SCA patients an advantage that allowed them not to elevate anxiety because the media have strong effects on anxiety, distress, and concern on pandemic days [31]. Some patients encountered difficulties and disruption in routine medical services due to health policies for COVID-19 prevention [32]. This undesired situation may worsen anxiety among patients with chronic diseases, but we did not observe greater state anxiety in this study. SCA patients in the present study were able to reach the second author easily by phone and received medical consultancy every time they needed it. Additionally, the Turkish healthcare system did not face the risk of collapse and provided chronic patients with health services without any problem. The numbers of cases and deaths were less alarming in Turkey than most European countries or the United States, and Mersin was not announced among the very high-risk cities [3]. We can therefore assume that patients in this study felt safe, trusted the healthcare services, and did not experience increased anxiety or worse clinical course during the COVID-19 outbreak.

Patients with SCA have been reported to be highly susceptible to a severe COVID-19 course [33]. In a recent report from France, COVID-19, even if potentially severe, did not seem to carry an increased risk of morbidity or mortality in patients with SCD. A vaso-occlusive crisis can complicate COVID-19 infection [34]. Sufficient literature data for COVID-19 are still lacking in pediatric, adolescent, and young adult patients with SCD. In this study, three patients had fever and/or respiratory symptoms during the outbreak, but none of them tested positive for SARS-CoV-2. Our single-center results demonstrated that adolescent and young adult SCA patients had a similar history of vaso-occlusive crisis and blood/exchange transfusion requiring hospitalization during the same period of two sequential years, 2019 and 2020. It can be argued that our patients were protected from COVID-19 by national outbreak management policies such as a curfew for people younger than 20 years of age and lockdown for others, and that they did not experience significant state anxiety and consequently had an ordinary clinical course. As far as we know, there is no published literature discussing the course of SCD during the SARS or MERS outbreaks.

The most important limitation of the present study is the small size of the sample from only one medical center. Larger sample sizes in multicenter SCD studies may assess anxiety status concurrently with COVID-19-related stressors (such as physical distancing, stay-at-home orders), secondary adversities (such as family dysfunction, economic and learning loss), media use, and social support characteristics. The STAI may not clearly differentiate anxiety disorders from depressive disorders, especially in older adult and psychiatric patients [35–37]. This study was conducted among adolescents and young adults who did not have a psychiatric diagnosis, but not taking depression into account is another limitation. We did not monitor psychosocial needs or scale coronavirus anxiety; nor did we do repeated evaluations in this study. We simply presented a number of descriptive COVID-19-related experiences in patients with SCD.

5. Conclusion

During the COVID-19 outbreak, the frequency of anxiety in adolescent and young adult SCD patients seems similar to the general population, and patients did not experience state anxiety greater than trait anxiety. To develop screening and support strategies for mental health needs, and to manage physical and mental health integration in pandemic conditions, further SCD studies should be conducted. We believe that outbreak anxiety scales should be developed for vulnerable people of all ages.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

None
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