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REVIEW

HIV-related stigma: effects on health outcomes and directions for stigma-focused interventions

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ABSTRACT

HIV-related stigma is a widespread experience among HIV-affected individuals that may have an impact on the well-being of both people living with HIV (PLWH) and associated individuals. This review examines the multifaceted nature of HIV-related stigma by summarizing its dimensions. Furthermore, it discusses how different dimensions of HIV-related stigma and intersectional stigma due to co-existing stigmatized conditions can lead to differential effects on the mental and physical health outcomes of PLWH. The scope of this review consists of the associations between HIV-related stigma and mental health challenges of depression and anxiety, as well as substance use, with a focus on the cognitive behavioral underpinnings, social isolation, and health behaviors of PLWH. On the other hand, the interplays between HIV-related stigma and immunological parameters, such as CD4 counts and viral loads, were discussed, which may have an effect through behavioral and non-behavioral pathways. This review also discusses possible stigma-informed policies and interventions with a multi-level approach. Specifically, it suggests that the focus of structural-level interventions can constitute policy regulations to ensure reducing HIV-related stigma and stereotype threats in organizational and legal settings. Stigma-informed intrapersonal interventions may focus on providing strategies that can target the cognitive and behavioral experiences of HIV-affected individuals through individual or group therapies. Lastly, interventions that focus on interpersonal and intergroup experiences can underline improving the quality of the contact and relationship between PLWH and HIV-negative individuals to challenge HIV-related stigma and improve the well-being of both populations.

Keywords: HIV-related stigma, mental health, physical health, stigma-informed interventions

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INTRODUCTION

Human immunodeficiency virus (HIV) compromises the immune system and can lead to a potentially life-threatening and chronic condition of acquired immunodeficiency syndrome (AIDS) if not managed properly [1]. According to the latest but underestimated numbers, approximately 40 million individuals worldwide are living with HIV, and 1.3 million people have acquired HIV in 2023 [2]. Although there has been great progress in each pillar of the HIV care cascade, especially in access to antiretroviral treatment (ART), with almost 21 million lives saved within the last two decades, many other challenges remain in HIV management. One of the major challenges is HIV-related stigma and discrimination and the associated psychosocial difficulties in people living with HIV (PLWH). The current review aims to discuss social stigma and its relations with mental and physical health outcomes, as well as intervention approaches to improve and protect the well-being of PLWH and associated individuals.

HIV-related stigma

Stigma is a social construction that refers to marking and devaluing individuals who possess attributes, conditions, or behaviors that are perceived as discrediting and contrary to the norms of social groups [3,4]. HIV-related stigma encompasses negative attitudes, including prejudices and stereotypes about HIV and discrimination toward PLWH [5]. HIV is widely stigmatized due to its association with practices that are perceived as immoral, such as unprotected or non-heterosexual intercourse or intravenous drug injection, its chronic nature, and misinformation related to the disease and its transmission [6,7].

HIV-related stigma can lead to psychological distress as well as exacerbate existing mental health difficulties in many PLWH [8]. In fact, the prevalence of mood disorders, such as depression and anxiety disorders, is elevated in PLWH compared to the general population [9]. HIV-related stigma is theorized to have several mechanisms and dimensions through which it leads to adverse social, physiological, and mental health outcomes [10-12].

HIV-related stigma dimensions

Enacted or experienced HIV stigma comprises experiences that include prejudice, negative attitudes, and discrimination toward PLWH [13]. In other words, enacted HIV stigma pertains to the public's explicit and disgracing behaviors or attitudes toward PLWH. These stigmatizing experiences are overt and obvious. However, stigma can also be executed covertly and implicitly. This type of stigma is known as microaggression. Primarily developed within the context of racial stigma, microaggression has been extended to HIV and conceptually covers stigmatizing behaviors and attitudes toward PLWH that are carried out subtly [14]. For instance, some individuals might possess implicit and unfounded beliefs that HIV implies dirtiness, and thus, these people might inaccurately label PLWH as "dirty" [15]. Not all individuals may explicitly admit that they have this assumption. However, this stereotype can still manifest itself through tacit behaviors, such as saying that an individual is "clean" to indicate their HIV-negative serostatus [14].

Under some circumstances, these experiences of enacted stigma and microaggressions can be internalized, meaning that negative and stigmatizing public attitudes and characteristics related to HIV can be accepted as applying to oneself (i.e., internalized or self-stigma; [16,17]). This internalization process is usually accompanied by several changes in cognitive, affective, and behavioral domains, which are responsible for mental and physical health difficulties [18]. For example, in a cognitive domain, internalization of stigmatizing attitudes, stereotypes, and prejudices might result in self-deprecating thoughts, including blaming oneself because of one's HIV serostatus and low levels of self-acceptance and self-worth [12,19,20]. From an affective perspective, internalized HIV stigma is associated with feelings of shame, guilt, embarrassment, depression, anxiety, and hopelessness [18,21,22]. According to cognitive behavioral theories, these negative self-related cognitions and emotions also have behavioral manifestations [23]. Within the context of HIV, these behavioral consequences of internalized HIV stigma include using maladaptive and dysfunctional coping skills, including avoidance, denial, and low adherence to treatment [24,25].

Another HIV-related stigma dimension that is associated specifically with health outcomes is anticipated HIV stigma, which refers to the expectations of PLWH that they will receive adverse and stigmatizing treatment if their positive HIV serostatus is known [12]. Researchers suggest distinguishing the sources of anticipated and enacted stigma, such as family members, friends, community members, and healthcare providers [12]. This conceptual separation allows researchers to predict the effects of anticipated and enacted HIV stigma more precisely.

Experienced, anticipated, and internalized HIV-related stigma were proposed by Earnshaw and Chaudoir [11] as part of the HIV stigma framework, which is helpful in understanding the effects of different types of stigma dimensions on health outcomes. Furthermore, initially originating from Berger et al.'s [26] HIV-related stigma scale, Turan et al. [12] modified this framework by adding perceived community stigma, which refers to the

PLWH's perception of whether the stigmatizing attitudes and behaviors related to HIV exist within their community and the degree of its severity. Perceived community stigma emphasizes the personalized nature of stigma; it incorporates perceptions of PLWH rather than actual experiences of discrimination, unlike enacted or experienced stigma [12].

Previous research focused on how these dimensions of HIV-related stigma are associated with different intrapersonal and interpersonal outcomes. However, recent studies on intersectional stigma emphasize the importance of considering other co-existing stigmatized conditions that PLWH can identify with to get a holistic view of their experiences [27]. The concept of intersectional stigma refers to the convergent stigmatizing attitudes and discrimination experienced by individuals who identify with several stigmatized social groups and their joint effects on the well-being of these marginalized social groups [28]. For instance, PLWH, who also identify as gay, can be subject to stigmatization because of their intersecting HIV serostatus and gay identity [29]. Specifically, they can experience both HIV-related stigma and homophobia, which might exacerbate stigma-induced difficulties [30]. In addition to their HIV serostatus, PLWH can also be stigmatized because of substance use [31] and identifying with racial/ethnic minorities [32]. These intersecting identities and stigmas can synergistically affect the health outcomes of PLWH [27,33]. Therefore, it is crucial to consider the possible vulnerabilities created by multiple stigmatized identities in understanding the experiences of PLWH.

Stigma is not imprinted on or inherent in a social group; it is a social construction that is developed through social interactions [34]. It includes the relational systems that surround stigmatized social groups. Through learning and conditioning processes, individuals from these systems might be associated with stigmatized social groups [35]. Thus, stigmatization may not be specific to individuals with stigmatized characteristics or conditions. People who are associated with stigmatized populations can also be subject to stigmatization, called stigma by association, courtesy stigma, or associative stigma [35]. Within the context of HIV, stigmatization can be directed toward family members and romantic partners of PLWH, healthcare providers who work with PLWH, and even individuals who are in the coincidental presence of PLWH [35-38]. It is particularly essential to consider stigma by association since it suggests that HIV-related stigmatization can include automatic reactions that can go beyond PLWH. In other words, HIV-related stigma can act like an infection, leading to a "social epidemic" [39].

HIV-related stigma and physical health outcomes

Stigma can be a stressor that affects the well-being of PLWH and individuals who are associated with them [40]. Different dimensions of stigma might have differential and adverse effects on physical and psychological health outcomes. The HIV stigma framework, developed by Earnshaw and Chaudoir [11], suggests that internalized HIV stigma can be a better predictor of mental health outcomes, whereas enacted and anticipated HIV stigma can be better predictors of physical health outcomes [12,13].

One of the immunological parameters that is studied within the context of HIV-related stigma is CD4 counts. Research supports the role of stress on declines in CD4 counts, indicating compromised immune health [41,42]. Considering that HIV-related stigma can be a chronic stressor, previous studies in the pre-ART era observed independent associations between enacted and anticipated HIV stigma with decreased CD4 counts [13]. However, it is essential to note that some studies have reported associations between depression and lower CD4 counts [41]. Thus, it is possible that in addition to HIV-related stigma, CD4 counts can be influenced by comorbid disorders, such as depression, among PLWH.

Viral load (HIV viral RNA level) can also be studied to observe the links between HIV-related stigma and psychological well-being. Viral load is the major predictor of favorable outcomes in PLWH. In addition, people with a suppressed viral load do not transmit the virus to their sexual partners [43]. Consistent with the HIV stigma framework, studies support the predictor role of enacted HIV stigma on viral load. However, research has observed positive associations between HIV-related stigma and unsuppressed (i.e., detectable) viral load [44,45], and specifically, high levels of enacted HIV stigma predicted higher viral load [46]. Thus, HIV-related

stigma might indirectly contribute to the risk of HIV transmission by making it hard to obtain an undetectable viral load.

PLWH can use behavioral and non-behavioral pathways through which HIV-related stigma can influence virological and immunological parameters [12]. One of the behavioral pathways that might lead to poor health outcomes is coping strategies used by PLWH to deal with HIV-related stigma. To manage HIV-related stigma, PLWH can use avoidant coping strategies, such as denying one's HIV serostatus through avoiding medications and HIV care visits, blaming oneself because of one's HIV serostatus, and behavioral disengagement from HIV treatment [47]. Avoidant coping strategies might result in PLWH disengaging from and not adhering to their treatment. Enacted and anticipated HIV stigma might be important when considering the behavioral pathway. Enacted and anticipated HIV stigma can have detrimental effects on CD4 counts and viral loads, potentially due to experiencing and anticipating stigma in healthcare settings, which can prevent PLWH from engaging in receiving adequate treatment [44].

Non-behavioral pathways refer to physiological and biological processes related to stress that can affect the clinical outcomes of PLWH. Anticipated HIV stigma, with a constant threat of being subject to stigmatization, enacted HIV stigma, and the stressors brought about by the infection, such as social isolation, can function as chronic stressors that compromise neuroendocrine and immune systems [48]. It has been proposed that chronic stressors and the perceived inability to cope with them can result in elevations in cortisol levels, indicating the dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis that is responsible for physiological stress responses [49,50]. These elevations in adrenal hormones can, in turn, lead to alterations in the functioning of the immune system, resulting in poor physical health outcomes among PLWH [51].

HIV-related stigma and mental health outcomes

HIV-related stigma not only contributes to adverse physical health outcomes but also has an impact on the mental health outcomes and psychological well-being of PLWH. One of the internalizing mental health difficulties that is investigated extensively in the context of HIV-related stigma is depression. Previous research has consistently replicated positive associations between HIV-related stigma and depression symptoms in PLWH [52]. However, there is no agreement on the direction of this influence [53]. Experiencing HIV-related stigma might contribute to depression symptoms, but experiencing depression symptoms might also lead PLWH to be more receptive and sensitive to perceiving stigma [54]. Furthermore, research has observed positive associations between HIV-related stigma and anxiety symptoms in PLWH [55]. Similar to depression symptoms, there might be a bidirectional relationship between anxiety symptoms and HIV-related stigma. In support of this, a meta-analysis reported that PLWH who were diagnosed with anxiety were more likely to report experiencing HIV-related stigma [56].

Considering different dimensions of HIV-related stigma, internalized HIV stigma has been observed to be a consistent predictor of depression and anxiety symptoms [53]. According to the cognitive behavioral theories, internalization of HIV-related stigma might lead to negative cognitions (e.g., blaming oneself because of one's HIV serostatus), emotions (e.g., guilt, shame), and maladaptive behavioral responses (e.g., avoiding treatment), which can contribute to developing or aggravation of the depression and anxiety symptoms in PLWH [19,57]. In addition to internalized HIV stigma, some studies suggest that enacted HIV stigma and perceived community stigma can indirectly contribute to depression symptoms through internalized HIV stigma [12,58]. Specifically, experiencing and perceiving stigma within one's community and the public can lead PLWH to internalize HIV-related stigma, which can then contribute to depression symptoms.

In addition to cognitive and behavioral models, the path through which HIV-related stigma predicts depression symptoms might be social isolation and non-disclosure of HIV serostatus that is brought about by stigma. Studies suggest that internalized HIV stigma leads PLWH to perceive social isolation or a lack of social support, which then predicts depression symptoms [59]. In other words, perceived social support and social isolation might be mediating variables in understanding the relationship between HIV-related stigma and depression symptoms. HIV-related stigma might also create barriers to disclosing one's HIV serostatus

[60]. Internalized HIV stigma has been observed to be predictive of non-disclosure [61]. However, it is essential to note that non-disclosure of one's HIV serostatus has also been found to be predictive of internalized HIV stigma and depression symptoms [61]. Thus, HIV-related stigma and disclosure of one's HIV serostatus might be feeding each other to induce an effect on depression symptoms.

Lastly, these complex relationships can be explained through understanding the health behaviors of PLWH. PLWH who have been self-stigmatizing might begin to avoid utilizing healthcare services because of the fear that they will be subject to stigma and discrimination from healthcare workers [62,63]. For this reason, they might be less likely to benefit from mental health services or adhere to the treatment if they receive any [64]. The avoidance of utilization of mental health services can explain the high levels of depression and anxiety symptoms observed in PLWH. There is also a possibility that experiencing stigma, combined with a lack of mental health support, can deprive PLWH of learning and practicing more functional and adaptive coping strategies, which can eventually contribute to mental health difficulties [65].

Substance use disorders have also been studied in the context of the health consequences of HIV-related stigma. Particularly in the United States and eastern Europe, substance use is a bigger problem among PLWH than in the general population [66,67]. One reason for the increased use of substances among PLWH can be that substance use might be one way of avoidant coping that PLWH benefit from to handle the stressors and negative emotions brought about by HIV and HIV-related stigma. For example, emotional dysregulation that is accompanied by depression symptoms among PLWH can perpetuate substance use [68]. Therefore, some studies suggest a mediating role of depression symptoms in the relationship between HIV-related stigma and substance use. In other words, internalized and enacted HIV stigma might be contributing to depression symptoms, which then contribute to substance use among PLWH [66]. This finding supports the avoidant coping nature of substance use.

PLWH can also be subject to stigmatization because of using substances. In fact, one qualitative study reported that substance use stigma towards PLWH was more prevalent compared to HIV-related stigma [69]. This finding suggests the co-existence of and interaction between two different stigmatized conditions to impact health outcomes. Researchers investigating this interaction observed that the relationship between internalized HIV stigma and depression symptoms was strengthened with the presence of internalized substance use stigma [31]. In other words, HIV-related and substance use stigma might interact with each other to create synergistic effects on the mental health outcomes of PLWH, supporting an intersectional stigma framework. Overall, these findings indicate that PLWH might use substances to cope with HIV-related stigma, which increases the possibility of experiencing stigma due to substance use as well, leading to intersectional stigma.

Even though PLWH might use substances as a way of coping, it can create unique health difficulties within the context of HIV, such as contributing to the transmission of the disease through increased sexual risk behaviors, injection drug use, non-adherence to treatment, and suboptimal virological and immunological responses to ART [70]. The combined influences and intersectional stigmas of HIV and substance use might result in strengthening the perception of barriers to HIV treatment due to fear of stigmatization and result in a lower likelihood of seeking treatment for these health difficulties [71,72]. These findings indicate that substance use might be a mental health result of HIV-related stigma but can also contribute to further mental and physical health difficulties. Therefore, interventions designed for PLWH and individuals who are associated with PLWH should consider the comorbidity of substance use disorders and their potential health effects and promote adaptive coping skills that PLWH can use instead of substance use [73].

Stigma-informed interventions

Taking into account the pervasive stigma-related difficulties and their complex effects on mental and physical health, it is essential to utilize stigma-informed interventions at different levels to improve and protect the well-being and health outcomes of PLWH and individuals who are associated with PLWH [74]. In line with Bronfenbrenner's ecological model [75], some researchers utilized a multi-level approach to studying HIV-related stigma interventions and their effects. Considering that stigma research investigates

the effects of stigmatization on different levels (e.g., intrapersonal, interpersonal, structural) and their intersections, it is beneficial to take a similar multi-level approach to study the effectiveness of HIV-related stigma interventions [76]. This section will briefly focus on the interventions developed to combat HIV-related stigma from intrapersonal, interpersonal, and structural levels and propose a new interpersonal-level discussion to potentially further ensure the wholeness of the intervention designs and implementations.

Structural-level HIV-related stigma interventions mainly focus on legislative changes in policies and governmental practices to ensure the involvement of PLWH in the communities. In their review, Cook et al. [77] reported several ways through which HIV-related stigma can be addressed at a structural level. Specifically, communicating values related to diversity and inclusivity within organizations and from organizational and political leaders may help reduce HIV-related stigma and its adverse effects by ensuring that the environment is devoid of stereotypical beliefs. This may enable PLWH to perform and work in environments that are free from stereotype threat. Furthermore, legal and policy interventions can be improved to ensure that the rights of PLWH are protected. Most studies on HIV-related stigma have been conducted in Western countries and Africa, which may show differences compared to non-Western countries. Therefore, more research is needed to elucidate cultural factors in the levels and effects of stigma to provide policies and interventions that are unique to the cultural needs of HIV-affected individuals. Specifically, in the context of Türkiye, there are no reported national policies and legal interventions to combat HIV-related stigma [78,79]. Even though PLWH should be benefiting from patient rights, one of the non-governmental organizations in Türkiye that works with HIV-affected individuals observed that compared to previous years, in 2023, PLWH encountered increased violations of their rights to healthcare access [80]. Furthermore, this violation had an intersectional nature, encompassing the violation of rights related to employment, travel, and housing due to HIV-related stigma and discrimination [80]. However, various non-governmental organizations in Türkiye are working in the area of battling HIV-related stigma through activism and educational interventions that utilize mass media and advertising, as well as providing legal counseling to PLWH. It is important to note that even though there are no specific legal policies tailored to address HIV-related stigma in Türkiye, interventions at different levels and their effects may reach and contribute to the structural level [77].

In addition to structural-level interventions, most researchers have focused on interventions at an intrapersonal level. Intrapersonal-level interventions mostly emphasize reducing the impact of HIV-related stigma, specifically internalized HIV stigma, on stigmatized individuals' physical and mental well-being, as well as individual behavior change through enhanced coping skills [77,81]. One of the interventions that is aimed at improving the well-being of PLWH is cognitive-behavioral therapy (CBT) interventions and counseling [79]. CBT techniques can be utilized in various stages of living with HIV, ranging from getting a diagnosis to managing HIV-related stigma. Within the context of HIV-related stigma, CBT-based interventions and counseling may be particularly useful in the process of preventing the internalization of HIV-related stigma [81]. The cognitive component of CBT may help challenge the stigmatizing cognitions and thoughts (e.g., "I am a bad person because I live with HIV") that lead to the internalization of HIV-related stigma by replacing them with thoughts that are based on more grounded and factual information, which may also include educational intervention strategies. In addition, the behavioral component of CBT may improve coping skills to use active coping strategies and facilitate stress management [82]. CBT strategies can also be administered in a group setting (i.e., support groups), which promotes the social integration of PLWH and eventually restores a sense of community and belonging crucial for treatment adherence [77].

Lastly, HIV-related stigma interventions can also be handled at an interpersonal- and intergroup-level. Interpersonal- and intergroup-level interventions mainly focus on considering the power of situational factors in the effects of HIV-related stigma [77]. In other words, these interventions consider the social factors to counteract the effects of stigma. Studies in this area mostly focused on reducing stigmatizing behaviors in non-stigmatized populations (i.e., "stigmatizers"), which is essential for reducing damaging stereotypes and stigma associated with HIV, as well as discrimination. It has

been suggested that stigma may be driven by a lack of outgroup contact [77]. Within the context of HIV, a lack of interaction between PLWH and non-stigmatized populations may be partly responsible for the stigma attached to HIV and PLWH by contributing to the continuation of commonly held negative stereotypical ideas. It has been suggested that aiding high-quality contact and interaction between PLWH and non-stigmatized groups may reduce the widespread stigma through exchanging information related to HIV and PLWH [76]. This bi-directional learning process between PLWH and non-stigmatized individuals may provide an opportunity to challenge misinformation and myths about HIV. Furthermore, PLWH may also get support and care from their close relationships, such as their family members, partners, and even healthcare workers. Therefore, it is also essential to provide educational interventions that incorporate strategies for engaging in functional coping strategies to individuals who are caring for and supporting PLWH that will help handle the unique difficulties of HIV and associated stigma [81]. It is important to note that just like PLWH who are affected by HIV-related stigma, individuals who are associated with PLWH may also get physically, emotionally, and socially affected by HIV-related stigma by association. For this reason, future research may also benefit from considering the mental and physical health outcomes, as well as relationship experiences of individuals who are associated with PLWH, to better understand how HIV-related stigma may impact different populations who are caring for and supporting PLWH.

CONCLUSION

This review aimed to provide an overview of HIV-related stigma dimensions and their effects on mental and physical well-being. Furthermore, it aimed to provide information on current developments in stigma-informed interventions at different levels of study in the context of Türkiye. Individuals who are affected by HIV are prominently subject to various types of stigmas that can have a differential impact on mental and physical health outcomes. In addition to HIV-related difficulties, consideration of intersecting health conditions and social identities of PLWH is essential to get a holistic understanding of their experiences and provide complementary interventions. Most interventions for HIV-related stigma and related difficulties are provided at the individual level by emphasizing psychotherapy to PLWH. However, it is known from stigma by association that the adverse effects of HIV-related stigma can be "contagious" to associated individuals, such as PLWH's partners or family members. Thus, future interventions can emphasize and incorporate the interpersonal relationships of PLWH into treatment and intervention processes. Lastly, even though awareness of HIV-related stigma, discrimination, and its adverse effects is increasing, more work is needed to be done at the structural level, such as improved and inclusive policies to enhance community involvement of PLWH and the welfare of societies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Nutrition-related infodemic experiences of the adults admitted to a Family Health Center in Ankara, Türkiye

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ABSTRACT

Objective: The infodemic has been a global challenge in almost all aspects of life, including nutrition-related practices. Dissemination of infodemic originating from both online and offline sources might end with risky health behaviors. Defining the case provides an opportunity to manage the infodemic. In this study, we aimed to define the nutrition-related infodemic experiences of the individuals over the age of 18 who applied to a Family Health Center in Ankara.

Materials and Methods: This descriptive study investigated individuals admitted to the Family Health Center in Ankara, Türkiye, with data collected through a questionnaire developed by researchers and face-to-face interviews conducted between May and July 2023. Data analysis utilized SPSS version 23.0, employing binary logistic regression to assess associations between various variables and infodemic management.

Results: The study, involving 222 participants, involved a majority of females (63.1%), married individuals (65.3%), and non-working participants (62.9%). Health-related characteristics indicated that 44.4% had diagnosed diseases, while 64.9% engaged in physical exercise meeting World Health Organization recommendations, and 25.8% reported tobacco use. Infodemic exposure was notable, with 51.8% always checking information sources, and logistic regression revealed a significantly higher infodemic experience among individuals with diagnosed diseases (OR = 3.621, 95% CI 1.244 to 10.545, p = 0.018).

Conclusion: In summary, our study suggests the presence of an infodemic related to nutrition behavior within healthcare environments. Based on these findings, we advocate for proactive measures and structured initiatives to address infodemic challenges in healthcare settings. Moreover, we encourage future investigations to delve deeper into the underlying dynamics of this phenomenon.

Keywords: infodemic, nutritional status, patients

INTRODUCTION

Infodemic is known to cause risk-taking behaviors that have the potential to harm health [1]. Infodemic can be in a physical and/or digital environment and include misinformation, disinformation, information voids, rumors, and conspiracy theories [2]. During the Coronavirus Disease 2019 (COVID-19) period, awareness about infodemic has gained momentum and infodemic management has been identified as a global priority by the Director of the World Health Organization (WHO) [3].

In its broader sense, infodemic has been studied on different health and disease-related topics, including noncommunicable diseases (NCDs). Noncommunicable diseases are responsible for almost 74% of deaths globally, and they include heart disease, stroke, cancer, diabetes, and chronic

lung disease. Unhealthy diets are among the major risk factors for NCDs [4]. Infodemic on unhealthy diets and nutrition-related topics may threaten health and cause unwanted consequences. In this regard, infodemic management might play a vital role in combating diet related NCDs.

There are good efforts to tackle misinformation on NCDs [5]. Since the COVID-19 pandemic, the spread of nutrition-related infodemic is known to have increased, coming from different sources, including social media sources [6]. Producing evidence for misinformation and disinformation produced about NCDs and risk factors might be helpful in infodemic management.

Family Health Centers are the first-level health institutions providing both preventive and curative outpatient services. Health/disease concerns and information-seeking behaviors of the individuals using these institutions are thought to be like those of the general population. In this regard, we aimed to define the nutrition-related infodemic experiences of the individuals over the age of 18 who applied to a Family Health Center (FHC) in Ankara.

METHODS

This descriptive study was conducted among the admitters to the Family Health Center (FHC), located in Ankara. 18-year-olds and older people admitted to the FHC who volunteered to participate in the study were included in the study. The FHC consists of six Family Health Units, and the study was conducted in one of these units. During the study period, a total of 2,115 individuals over the age of 18 applied to the selected unit.No sampling calculation was performed in the research; it was conducted with volunteers who applied within the specified date range.

A questionnaire including 22 questions in three sections including sociodemographic characteristics, health and disease profiles and information/infodemic status of the participants was developed by the researchers. A pretiral of the questionnaire was completed among 20 participants and due to the feedback obtained, revision of the questionnaire was made. Face-to-face data collection was completed between May and July 2023. Written informed consent was obtained from the participants.

SPSS 23.0 was used for data entry and statistical analysis. Marginal tables were presented to define the basic characteristics. People who did not use tobacco, did regular physical activity compatible with the WHO recommendations, perceived their nutrition behavior as healthy, and perceived their health status as very sufficient were assessed as "live healthy." Binary logistic regression analysis (Backward LR) was performed to analyze the associations between the infodemic management experience and selected variables. Variables in the model were selected as having a diagnosed disease, sex, marital status, level of information about nutrition, and living a healthy lifestyle. The selection of the model for logistic regression was done due to the literature review and the statistically significant association between the infodemic management experience and Odds Ratios (95% CI) were estimated for each variable. A p value less than 0.05 (two-sided) was accepted as statistically significant. SPSS version 29.0 Statistics software (IBM Corp., Armonk, NY, USA) was used in the data analysis.

Both the institutional official permissions from the Ankara Health Directorate Scientific Research Committee (Number: E-771-00003010926, Date: 10.08.2023) and Hacettepe University Non-Interventional Clinical Research Ethics Committee (Number: GO 23/342, Date:18.04.2023) were obtained before data collection. Informed consent was obtained from all participants.

RESULTS

222 individuals participated in the study. In Table 1, selected socio-demographic features of the participants were presented. The majority of the participants were female (n=140, 63.1%), married (n=145, 65.3%), and not working (n=139, 62.9%). Among the total, 58.2% of the participants declared their income status equal to their expenditure (n=128).

In Table 2, the characteristics of the participants related to their health status and behaviors were

Table 1. Socio-demographic features of the participants

Feature	Number	Percent
Sex (n=222)		
Male	82	36.9
Female	140	63.1
Marital status (n=222)		
Married	145	65.3
Not married	**77**	**34.7**
Occupational status (n=221)		
No	**139**	**62.9**
Yes	**82**	**37.1**
Income status compared to expenditure (n=220)		
Less	**59**	**26.8**
Equal to	**128**	**58.2**
Exceeds	**33**	**15.0**

shown. 44.4% of the participants had a disease diagnosed by the doctor (n=99). The majority of the participants perceived their health as very healthy and healthy (n=132, 60.0%). Nutrition status was perceived as very healthy and healthy among 113 participants (50.9%). The majority of the participants perceived their level of knowledge as sufficient (n=121, 56.0%). Perception of nutrition knowledge as sufficient among the total was 56.8% (n=125). Among the total, 64.9% of the participants were doing physical exercise compatible with the WHO recommendations (n=144). The tobacco use frequency was 25.8% (n=57).

Health and nutrition information sources of the participants were shown in Table 3. The Internet seems to be used as a frequent health and nutrition information source. Traditional newspapers, friends, and relatives are not very popular among information sources. TV channels, friends, and relatives follow internet-based sources used for both health and nutrition information.

In Table 4, participants' infodemic exposure and spreads risks were presented. Among the total, 51.8% of the participants always check the information source, 57.5% always check if the information is true, 44.1% always check if the information is updated, and 52.7% always share the information only if they are sure that it is true. There were participants sharing information with others without doing anything.

Table 2. Health status and behaviors of the participants

Feature	Number	Percent
Disease diagnosed (n=222)		
No	123	55.4
Yes	99	44.6
Use medicine (n=221)		
No	137	62.0
Yes	84	38.0
Perception about health status (n=222)		
Very healthy	17	7.7
Healthy	116	52.3
Not sure	53	23.9
Unhealthy	34	15.3
Very unhealthy	2	0.9
Perception about nutrition status (n=222)		
Very healthy	10	4.5
Healthy	103	46.4
Not sure	65	29.3
Unhealthy	41	18.5
Very unhealthy	3	1.4
Level of knowledge about health (n=216)		
Sufficient	121	56.0
Could not decide	41	19.0
Insufficient	54	25.0
Level of knowledge about nutrition (n=220)		
Sufficient	125	56.8
Could not decide	47	21.4
Insufficient	48	21.8
Physical activity status in accordance with WHO definition (n=222)		
Yes	144	64.9
No	78	35.1
Tobacco use (n=221)		
Never	120	54.3
Quitted	44	19.9
Currently use	57	25.8

Infodemic experience of the participants and their friends and relatives were presented in Table 5. Among the total, 18 participants had infodemic experience (8.1%). The frequency of infodemic experience of the participants' friends or relatives was 15.5% (n=34).

Table 3. Health and nutrition information sources of the participants (%)

Source	Always	Sometimes	Could not decide	Rarely	Never
Health information source					
TV (n=222)	18.9	36.0	1.4	18.5	25.2
Radio (n=219)	4.1	16.0	3.7	17.4	58.9
Traditional newspaper (n=220)	7.7	14.5	4.1	19.1	54.5
Internet-news (n=220)	**42.7**	**32.3**	3.2	10.9	10.9
Internet-any source (n=220)	**39.1**	**34.1**	4.1	7.7	15.0
Popular book (n=220)	6.8	22.3	6.8	24.5	39.5
Scientific paper (n=221)	10.4	22.6	5.0	18.6	43.4
Scientific book (n=220)	8.6	19.5	4.5	21.8	45.5
Friend (n=222)	24.3	40.1	8.1	14.4	13.1
Relative (n=222)	20.7	33.3	6.3	14.4	25.2
Nutrition information source					
TV (n=220)	20.9	36.8	1.8	14.5	25.9
Radio (n=219)	4.6	16.7	3.7	16.7	58.3
Traditional newspaper (n=220)	6.9	16.1	3.7	15.6	57.8
Internet-news (n=220)	**43.1**	**31.5**	3.7	9.3	12.5
Internet-any source (n=220)	**38.1**	**32.6**	3.7	10.1	15.6
Popular book (n=220)	7.8	18.8	8.3	20.6	44.5
Scientific paper (n=221)	10.1	22.0	4.6	18.3	45.0
Scientific book (n=220)	9.3	20.8	5.6	18.5	45.8
Friend (n=222)	19.7	41.7	6.9	14.7	17.0
Relative (n=222)	17.1	34.7	7.9	16.2	24.1

Table 4. Participants' infodemic exposure and spread risk (%)

Risk	Always	Sometimes	Could not decide	Rarely	Never
Check the information source (n=220)	**51.8**	30.0	4.1	5.5	8.6
Check if the information is true (n=221)	**57.5**	27.1	3.2	5.0	7.2
Check if the information is update (n=220)	**44.1**	33.2	6.8	6.4	9.5
Share the information with others without doing nothing (n=219)	7.8	21.5	13.7	13.7	**43.3**
Share the information with others if sure of its accuracy (n=220)	**52.7**	32.3	6.8	4.5	3.6

Table 5. Infodemic experience of the participants

Infodemic experience	Number	Percent
Personal experience (n=221)		
No	203	91.4
Yes*	18	8.1
About her/his current disease	*12*	
Food poisoning	*7*	
Experience of friends/relatives (n=220)		
No	186	84.5
Yes*	34	15.5
About her/his current disease	*17*	
Food poisoning	*16*	
**one experience detail is missing*		

In Table 6, infodemic experience of the participants is presented due to selected variables. Females, single people, and people with no children had an infodemic experience that was higher compared to males, married people, and people who had children ($p>0.05$). Participants with a diagnosed disease and used medicine had an infodemic experience with a higher frequency compared to those without a disease diagnosis ($p=0.015$). Participants who did not use medicine or control information sources and had a low level of health information had more infodemic experience compared to the others ($p>0.05$). People who lived healthy had a lower frequency of infodemic experiences than the participants who lived unhealthy ($p>0.05$).

Table 6. Features in association with infodemic experience

Variable	Infodemic experience				p
	No		Yes		
	Number	Percentage	Number	Percentage	
Sex					
Male	76	92.7	6	7.3	0.730
Female	127	91.4	12	**8.6**	
Marital status					
Married	135	93.1	10	6.9	0.349
Not married	68	89.5	8	**10.5**	
Have children					
No	76	89.4	9	**10.6**	0.294
Yes	127	93.4	9	6.6	
Physical activity (sufficient)					
No	71	91.0	7	**9.0**	0.739
Yes	132	92.3	11	7.7	
Currently tobacco use					
No	**152**	**92.7**	**12**	**7.3**	0.423
Yes	**50**	**89.3**	**6**	**10.7**	
Disease diagnosed by the doctor					
No	**117**	**95.9**	**5**	**4.1**	**0.015**
Yes	**86**	**86.9**	**13**	**13.1**	
Medicine use					
No	**131**	**95.6**	**6**	**4.4**	**0.08**
Yes	**71**	**85.5**	**12**	**14.5**	
Level of information about health (sufficient)					
Yes	**114**	**94.2**	**7**	**5.8**	**0.139**
No	**86**	**88.7**	**11**	**11.3**	
Level of information about nutrition (sufficient)					
Yes	**114**	**91.9**	**10**	**8.1**	**0.924**
No	**87**	**91.6**	**9**	**8.4**	
Control information source (always/sometimes)					
Yes	**166**	**92.7**	**13**	**7.3**	**0.276**
No	**35**	**87.5**	**5**	**12.5**	
Live healthy*					
Yes	**55**	**93.2**	**4**	**6.8**	**0.654**
No	**148**	**91.4**	**14**	**8.6**	

*Participants who do not use tobacco products, do physical exercise, perceive health status as very good and good, perceive nutrition behaviour as healthy

In Table 7, the existence of an infodemic experience is presented by having a diagnosed disease. Infodemic experience was statistically significantly higher among the people who had a diagnosed disease compared to the ones with no disease (OR=3.621, 95% CI 1.244 to 10.545, p=0.018).

Table 7. Logistic regression model for features in association with infodemic experience

Diagnosed disease	OR	95%CI	p value
No (ref)	**1.00**		
Yes	**3.621**	1.244-10.545	0.018

**Adjusted for sex, marital status, level of information about nutrition, living healthy*

DISCUSSION

We aimed to define the nutrition-related infodemic experiences of individuals over the age of 18 who applied to a Family Health Center in Ankara. In the study conducted for this purpose, it was found that infodemic, which is known to cause risk-taking behaviors that have the potential to harm health [1], was defined by 18 participants (8.1%). The frequency of the infodemic experience of the participants' friends or relatives was 15.5% (n=34) (Table 5). Infodemic also known as "too much information," including misinformation, disinformation, information voids, conspiracy theories, etc., can cause harm [2]. The difference might be due to the fact that people may refrain from speaking about their own experiences. Or friends' infodemic experiences might have caused a memorably serious health problem, and they might have been more memorable for the participants.

Infodemic experience might be associated with a number of variables. We tried to investigate possible variables in our research. Within all, only participants with a diagnosed disease and used medicine had an infodemic experience with a higher frequency compared to those without a disease diagnosis (Table 6). However, the logistic regression model only confirmed the diagnosed disease variable (Table 7). Although the descriptive feature of the study does not allow us to present the cause-and-effect relationship between the variables, people with a diagnosed disease might have experienced an infodemic due to their health-seeking behavior from different sources, and this might have caused an infodemic experience. This is in line with findings by Scalvedi et al., which highlighted the reality that nutritional knowledge has a direct impact on eating habits and concluded that individuals with medical conditions can voluntarily seek information, increasing their ability to obtain misinformation [7]. Prieto also emphasized the reality that contradictory eating advice during the COVID-19 pandemic led to confusion and anxiety, primarily among risk groups [8]. The Internet seems to be the most frequent source of health and nutrition information, and TV channels, friends, and relatives follow internet-based sources used for both health and nutrition information. The traditional newspaper, friends, and relatives are not very popular among information sources (Table 3). Nutrition is among the popular misinformation themes spreading via social media. In their systematic review, Suarez-Lledo and Alvarez-Galvez found that 36% of the misinformation on diet-related issues has been found as 36% [9]. In this regard, examining infodemic related to diet and nutrition might contribute to better understanding the background dynamics. Denniss et al. pointed out the disparity between the accuracy and quality of the content on the internet with regard to nutrition, supplementing evidence that participants using multiple sources are more likely to be exposed to infodemics [10].

Wang et al. recommended examining the susceptibility of different groups to misinformation in their research conducted in 2012 [11]. Accordingly, Ruani and Reiss demonstrated that susceptibility to COVID-19 nutrition misinformation was linked to changes in food behaviors, particularly among people with reduced health literacy [12]. Their cross-sectional web-based survey indicated that exposure to false information influenced dietary choices, reflecting the importance of interventions addressing optimum critical thinking skills development in determining nutrition-related information. These findings further consolidate the importance of our study to ascertain the effect of misinformation on health-related action in different populations. Our research might have responded to this recommendation as it was conducted among the admitters of a FHC limited to their socio-demographic features and health/disease profiles (Table 1 and Table 2).

Almost one out of two participants (51.8%) always checked the information source. Additionally, 57.5% always check if the information is true, 44.1% always check if the information is updated, and 52.7% always share the information only if they are sure that it is true (Table 4). Results confirm that there is a need to support the participants in terms of infodemic management. Raising awareness and increasing the health and digital literacy

capacity of the participants might be helpful in this regard [2,13]. The complexity of the information environment [3,14] is a challenging issue, however, trusted and scientific-based methodologies will be helpful to reach our different populations either physically or digitally.

Our study has also strengths and limitations. Searching nutrition related infodemic status in a health center has been the strength of the study. We had a couple of limitations. The descriptive feature of the study has been a limitation and does not allow us to generalize the results. The participants' self-perception might not be as objective as they are observed through their real-life experiences. The number of participants did not allow us to conduct detailed further analysis.

In conclusion, we think that the study results are giving clues on the existence of infodemic related to nutrition behavior in health settings. In light of our findings, we recommend responding and organizing infodemic management activities in health settings. Additionally, further research is recommended to be carried out to better understand the dynamics.

Author contribution

Study conception and design: DA, DAB, EÇK, EA, and SEA; data collection: EÇK, EA, and SEA; analysis and interpretation of results: DA, DAB, EÇK, EA, and SEA; draft manuscript preparation: DA, DAB, EÇK, EA, and SEA; critical reading of the manuscript: DA, DAB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Number: GO 23/342, Date: 18.04.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Association of HIF-1α and TNFα single nucleotide polymorphisms with periodontal disease in diabetic patients

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ABSTRACT

Objective: Periodontal disease is a prevalent chronic inflammatory condition affecting the supporting structures of teeth and is considered one of the chronic complications of Type 2 diabetes mellitus (T2DM). Both diabetes and periodontal diseases are complex, multifactorial diseases to which genetic factors play a crucial role in susceptibility. The TNF-α/HIF-1 pathway might have a regulatory function in periodontal tissues. Several case-control studies have examined the association between TNF-α G308A or HIF-1α C1772T polymorphisms and diabetes complications, but the results have been inconsistent. We aimed to investigate the association between two specific genetic variants -HIF-1α C1772T and TNF-α G308A- and periodontal disease in patients with type 2 diabetes.

Methods: A total of 109 individuals were enrolled in the study including 24 chronic periodontitis with T2DM (group 1), 35 gingivitis with T2DM (group 2), 26 non-diabetic individuals with chronic periodontitis (group 3) and 24 periodontally healthy non-diabetic individuals (group 4). The normal allelic and genotype distribution of these variants was analyzed in healthy Turkish adults (n: 120), independent of the study cohort. Allele and genotype distribution of group 4 and healthy Turkish adults were similar. Allelic and genotypic comparisons between group 4 and other groups were evaluated by PCR-RFLP. Allelic, dominant, and recessive genetic models were calculated to assess the strength of the association.

Results: We found a significant association between the A allele at TNF-α G308A and the risk of gingivitis in T2DM (OR=3.75, CI:1.015–13.860, p=0.048). There was no association detected between HIF-1α C1772T polymorphisms and risk for periodontal diseases with T2DM.

Conclusion: These results suggest that TNF G308A polymorphism may be involved in the pathogenesis of periodontal disease in diabetics. Future studies may contribute to the investigation of the potential polygenic predisposition of the diseases and reinforce our findings.

Keywords: diabetes mellitus, periodontal disease, chronic periodontitis, gingivitis, single nucleotide polymorphism, HIF-1α, TNF-α, rs11549465, rs1800629

INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia. DM affects millions of people around the world with its rapidly increasing incidence and prevalence [1,2]. Along with the known macrovascular and microvascular complications, periodontal disease is considered to be one of the chronic complications of diabetes [3]. Periodontal disease is a multifactorial condition influenced by various genetic and environmental factors, and is characterized by the specific pathogenic bacteria colonized in the supporting tissues surrounding the teeth and the specific host response [4]. Diseases affecting the tooth-supporting structures are defined as gingivitis or periodontitis. The clinical features that distinguish periodontitis from gingivitis are the progressive destruction of the periodontal ligament and alveolar bone accompanied by periodontal pocket formation and/or gingival recession [5,6].

Inflammation is the key feature of both diabetes and periodontal diseases. Proinflammatory cytokines such as IL-1, and tumor necrosis factor-α (TNF-α) play a key role in the pathogenesis of periodontal diseases and inhibition of these cytokines reduces periodontitis-associated bone loss [7-10]. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor consisting of alpha and beta subunits [11,12]. Many cells respond to hypoxia and ischemia by increasing the HIF-1-dependent transcription of vascular endothelial growth factor and other angiogenic growth factors [13]. On the other hand, TNF-α is the main pro-inflammatory cytokine, and hypoxia increases TNF-α expression in various cells, including osteoblasts, which in turn activates the HIF-1α pathway [14].

Both diabetes and periodontal diseases are complex, multifactorial diseases to which genetic factors play a crucial role in susceptibility [2,6]. HIF-1α and TNF-α are key molecules involved in inflammatory and angiogenic processes, both of which are critical in the pathogenesis of periodontal disease and diabetes. Single nucleotide polymorphisms (SNPs) are the most common form of polymorphism and affect the function of the gene [15]. Several case-control studies have examined the association between TNF-α G308A (rs1800629) or HIF-1α C1772T (rs11549465) polymorphisms and diabetes complications, but the results have been inconsistent [16,17].

This study aims to evaluate the association between two specific genetic variants -HIF-1α rs11549465 and TNF-α rs1800629- and periodontal disease in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subject characteristics

The research was conducted as a single-center, cross-sectional, case-controlled cohort study at Hacettepe University. Fifty-nine patients with type 2 DM (T2DM) and 50 non-diabetic control individuals aged 30-65 were included in the study.

Patients were divided into four groups according to the presence of diabetes and periodontal disease;
Group 1: T2DM patients with chronic periodontitis (n:24),
Group 2: T2DM patients with gingivitis (n:35),
Group 3: Non-diabetic individuals with chronic periodontitis (n:26),
Group 4: Periodontally healthy non-diabetic individuals (n:24).

T2DM diagnosis was made according to American Diabetes Association criteria [1]. Patients were evaluated for microvascular and macrovascular complications. In the periodontology department, all parameters were evaluated in each patient for 6 teeth containing 6 mm or deeper periodontal pockets. If one of these teeth was absent in the mouth, the sampling was performed using the neighboring teeth with similar characteristics. Plaque index (PI), gingival index (GI), probing pocket depth (PPD), clinical attachment loss (CAL), and bleeding on probing (BOP) were recorded by a periodontal probe (Michigan O Color-Coded Probe, Hu-Friedy, Chicago, IL) for each tooth. The separated serum from the 10 ml blood was stored at -80 °C until tested for genotyping. This study (GO 14/250) was approved by the Non-Interventional Clinical Research Ethics Board of Hacettepe University. Informed consent was obtained from each patient.

Patients were excluded from the study if they had a diagnosed malignancy or paraproteinemia, were taking medications with known side effects on teeth or gums, had a history of preeclampsia or eclampsia during pregnancy, or had a history of ileus. Additional exclusion criteria included patients undergoing hemodialysis or peritoneal dialysis for chronic kidney disease, those with chronic liver disease, individuals outside the age range of 30-65 years, pregnant women, lactating women and active smokers.

Anthropometric parameters

Age, sex, height, weight, body mass index (BMI), blood pressure, and waist circumference were recorded.

Biochemical parameters

A1c level was measured by high-performance liquid chromatography method.

Genotyping analysis

In the Department of Medical Genetics, Hacettepe University, genotyping of TNF-α and HIF-1α was performed from the blood samples of a total of 109 participants.

To determine the genotype and allele distributions of HIF-1α, and TNF-α in the general population, polymorphism analysis of these genes was performed from the blood samples of 120 healthy individuals (37F/83M) in addition to these 109 participants. Thus, it was aimed at obtaining the normal allele and genotype distribution of these SNPs in healthy adults. Healthy individuals were selected among the hospital employees and the relatives of patients without any illness, who were referred to our department and willing to participate in the study.

1) DNA Extraction and PCR

Genomic DNA was extracted from peripheral blood using the salt precipitation method. The samples were stored at -80° C in an appropriate buffer solution. All Polymerase Chain Reactions (PCR) were performed using GoTaq Flexi DNA Polymerase (Promega, WI, ABD) at temperatures for optimal binding of primers.

2) Genotyping

a) TNFα (rs1800629)

Genotyping was performed by PCR + DNA Restriction Fragment Length Polymorphism (RFLP) method using 5'-AGG CAA TAG GTT TTG AGG GCC ATG-3' and 5'-ACA CAC AAG CAT CAA GGA TAC-3'. Obtained PCR products were subjected to StyI (Catalog no: R0500S, New England Biolabs, MA, ABD) DNA restriction enzyme.

b) HIF1 (rs11549465)

Genotyping was performed by PCR + DNA Restriction Fragment Length Polymorphism (RFLP) method using 5'-GAC TTT GAG TTT CAC TTG TTT-3' and 5'-ACT TGC GCT TTC AGG GCT TGC GGA ACT GCT T-3'. Obtained PCR products were subjected to NmuCI DNA restriction enzyme. The obtained PCR products will be subjected to Tsp45I (Catalog no: R0583L, New England Biolabs, MA, USA) DNA-cutting enzyme at 37 C.

All samples were genotyped by moving on agarose gel. The verification process was done for 20 samples by DNA sequence analysis method using the forward or reverse primers.

Statistical analysis

All statistical analyses were performed using the SPSS20.0 (SPSS software package, Chicago, USA). The Hardy Weinberg equation of the gene polymorphisms were analyzed by chi-square test. Linkage disequilibrium was evaluated with R software (genetics package). No relationship was detected between the SNPs. The comparison of the data of other frequency types by allele or genotype was done by chi-square test and odds ratio was calculated. Allelic, dominant and recessive genetic models were calculated to assess the strength of the association. A difference with a P value of <0.05 was considered as statistically significant. First of all, the normal distributions for all the continuous data were tested and logarithmic transformation was applied to non-normally distributed data. Continuous variables were expressed as mean and standard deviation. The differences between the groups were evaluated using the Student's t-test for normally distributed variables and the Mann-Whitney-U test for non-normally distributed variables. On the other hand, the Kruskal-Wallis test was used for the analysis of more than three

non-normally distributed groups, and paired comparisons were made with the Dunn test in case of a difference between the groups. Chi-square and Fisher's exact test were used for the evaluation of the categorical variables.

RESULTS

Comparison of Different Groups

Fifty-nine diabetic patients (36F/23M, mean age: 53.6±6.4) and 50 non-diabetic individuals (27F/23M, mean age: 41.0±8.5) were included in the study. As expected, the body weight (86.9±16.4 and 74.4±14.1 kg), BMI (34.6±7.2 and 26.8±4.7kg/m^2), and waist circumference (102.8±12.4 and 89.3±11.7 cm) in the diabetic group was statistically significantly higher than the non-diabetic group ($p<0.001$).

Eighty five patients with periodontal disease and 24 periodontally healthy patients were also compared. As expected, periodontal PD (4.0±1.9 mm), CAL (4.5±2.1 mm), PI (1.2±0.7), GI (1.6±0.6), BOP (95.8%) in the group with periodontal disease was statistically significantly higher than the patients without periodontal disease ($p<0.001$).

Thirty-five T2DM patients with gingivitis (27 F/8 M, mean age: 54.0±5.4) and 24 T2DM patients with chronic periodontitis (9 F/15 M, mean age: 51.3±7.8) were compared. While the age at diagnosis was 44.4±7.6 in the group with diabetic gingivitis, it was 45.2±7.7 in the group with diabetic periodontitis ($p=0.694$). There was no significant difference between fasting plasma glucose (158.2±61.7 mg/dL), postprandial glucose (184.4 ± 78.5 mg/dL), A1c levels (7.5±1.8%) of patients in the gingivitis group and those in the periodontitis group with fasting plasma glucose (173.0±60.7 mg/dL), postprandial glucose (219.2±89.2 mg), A1c levels (8.4±1.9%) ($p=0.174$; 0.132; 0.063, respectively). The mean BMI of the diabetic gingivitis group was 34.6±8.3 kg/m^2 and this is the group with the highest number of patients among the groups. The mean BMI was 33.0±5.8 kg/m^2 in the diabetic periodontitis group. On the other hand, the mean BMI of the non-diabetic periodontally healthy group, which we accepted as a reference and made the genotype and allele comparison of all groups accordingly, was found to be 25.3±2.7 kg/m^2. The mean PPD, CAL, and PI were higher in the diabetic periodontitis group than the non-diabetic periodontitis group, but there was no statistically significant difference.

Genotype and Allele Frequencies of HIF-1α, TNF-α in Adults

The normal frequency of genotype and allele distribution of HIF-1α and TNF-α in adults was intended to be seen with the 120 healthy individuals in the Medical Genetics Department's pool. Genotype and allele distribution of HIF-1α and TNF-α in the general population are shown in detail in Table 1. Each SNP was tested for Hardy-Weinberg equilibrium and all were in equilibrium. No association was detected between the HIF-1α – TNF-α SNPs.

Evaluation of TNF-α Polymorphism According to the Study Groups

The GG genotype, which is frequent in the population, was detected to be significantly less frequent in the diabetic gingivitis group ($p=0.026$). Similarly, the frequent G allele in the population was significantly less frequent in the diabetic gingivitis group ($p=0.013$) (Table 2). We showed that TNF-α G308A polymorphism is associated with an increased risk for gingivitis in T2DM patients. In other words, the risk of gingivitis was found to be 4 times higher in GA+AA carrier diabetic patients (OR=4.13, CI:1.0-16.6, $p=0.045$). In line with this, the risk of diabetic gingivitis was detected to be increased by approximately 4 fold in mutant A allele carriers (OR=3.75, CI:1.015-13.860, $p=0.048$). There was no statistically significant difference between the other groups.

Table 1. Genotype and Allele Frequencies of Hypoxia Inducible Factor-1α (HIF-1α) and Tumor Necrosis Factor-α (TNF-α) in the Turkish Population

HIF-1α (rs11549465) (n:120)		**TNF-α (rs1800629) (n:120)**	
Genotype		**Genotype**	
CC	76.6% (n:92)	**GG**	67.5% (n:81)
CT	20.8% (n:25)	**GA**	31.7% (n:38)
TT	2.5% (n:3)	**AA**	0.8% (n:1)
Allele		**Allele**	
C	87.1% (n:209)	**G**	83.3% (n:200)
T	12.9% (n:31)	**A**	16.7% (n:40)

HIF-1α: Hypoxia Inducible Factor-1alpha, TNF-α: Tumor Necrosis Factor-alpha, G: Guanine, C: Cytosine, A: Adenine, T: Thymine, n: Number of patients.

Table 2. Allele and Genotype Frequencies of TNF-α G308A polymorphisms (rs1800629) in the study groups

GENOTYPES	GG	GA	AA	P*
Non-DM/Healthy PS (Group 4)	87.5% (n:21)	12.5% (n:3)	0% (n:0)	
Non-DM/Periodontitis (Group 3)	80.8% (n:21)	19.2% (n:5)	0% (n:0)	0.445; 0.723
DM/Gingivitis (Group 2)	62.9% (n:22)	34.3% (n:12)	2.9% (n:1)	**0.026**; 0.140
DM/Periodontitis (Group 1)	75% (n:18)	25% (n:6)	0% (n:0)	0.237; 0.511
GROUPED GENOTYPES	**GG**	**GA + AA**		
Non-DM/Healthy PS (Group 4)	87.5% (n:21)	12.5% (n:3)		
Non-DM/Periodontitis (Group 3)	80.8% (n:21)	19.2% (n:5)		0.723
DM/Gingivitis (Group 2)	62.9% (n:22)	37.1% (n:13)		0.090
DM/Periodontitis (Group 1)	75% (n:18)	25% (n:6)		0.511
ALLELES	**G**	**A**		
Non-DM/Healthy PS (Group 4)	93.8% (n:45)	6.3% (n: 3)		
Non-DM/Periodontitis (Group 3)	90.4% (n:47)	9.6% (n:5)		0.438; 0.811
DM/Gingivitis (Group 2)	80% (n:56)	20% (n:14)		**0.013**; 0.221
DM/Periodontitis (Group 1)	87.5% (n:42)	12.5% (n:6)		0.228; 0.663

DM: Diabetes mellitus, PS: Periodontal status, n: Number of patients, G: Guanine, A: Adenine.

*All genotypes, grouped genotypes, and alleles were compared relative to Group 4, and p values were written in order.

Evaluation of HIF-1α Polymorphisms According to the Study Groups

HIF-1α genotyping was performed using the DNA samples of 109 participants in the study groups. First of all, the genotype and allele distribution in groups were analyzed. Because the HIF-1α TT genotype is very rare in the population, it was also grouped with CT heterozygotes. Our main objective was to evaluate the relationship between periodontal diseases in diabetes and HIF-1α. Allele and genotype frequencies of HIF-1α in the study groups are shown in Table 3. Intergroup comparisons were made between the non-diabetic, periodontally healthy group (group 4) and the other groups. All genotypes, grouped genotypes and alleles were compared relative to Group 4 and p values were written in order (Table 3). No statistically significant difference was observed between the groups (group 3 and others) in terms of the genotype and allele distribution of HIF-1α C1772T polymorphisms. Odds ratio and confidence interval (CI) were calculated for all groups setting HIF-1α CC genotypes (dominant model) as reference. There was no statistically significant difference between the groups.

Table 3. Allele and Genotype Frequencies of HIF-1α C1772T polymorphisms (rs11549465) in the study groups

GENOTYPES	CC	CT	TT	P*
Non-DM/Healthy PS (Group 4)	66.7% (n:16)	33.3% (n:8)	0% (n:0)	
Non-DM/Periodontitis (Group 3)	80.8% (n:21)	15.4% (n:4)	3.8% (n:1)	0.117 / 0.394
DM/Gingivitis (Group 2)	57.1% (n:20)	42.9% (n: 15)	0% (n:0)	0.397 / 0.465
DM/Periodontitis (Group 1)	66.7% (n:16)	20.8% (n:5)	12.5% (n:3)	>0.9 / 0.529 / 0.580
GROUPED GENOTYPES	**CC**	**CT + TT**		
Non-DM/Healthy PS (Group 4)	66.7% (n:16)	33.3% (n:8)		
Non-DM/Periodontitis (Group 3)	80.8% (n:21)	19.2% (n:5)		0.468
DM/Gingivitis (Group 2)	57.1% (n:20)	42.9% (n:15)		0.465
DM/Periodontitis (Group 1)	66.7% (n:16)	33.3% (n:8)		>0.9
ALLELES	**C**	**T**		
Non-DM/Healthy PS (Group 4)	83.3% (n:40)	16.7% (n:8)		
Non-DM/Periodontitis (Group 3)	88.5% (n:46)	14.3% (n:6)		0.282 / 0.837
DM/Gingivitis (Group 2)	78.6% (n:55)	21.4% (n:15)		0.393
DM/Periodontitis (Group 1)	77.1% (n:37)	22.9% (n:11)		0.372

DM: Diabetes mellitus, PS: Periodontal status, n: Number of patients, C: Cytosine, T: Thymine.

*All genotypes, grouped genotypes, and alleles were compared relative to Group 4, and p values were written in order.

DISCUSSION

Our study provides valuable insights into the genetic basis of periodontal disease in Turkish diabetic patients. Our study showed that TNF-α G308A polymorphism is associated with an increased risk for gingivitis in T2DM patients. The risk of diabetic gingivitis was found to be increased by approximately 4-fold in mutant A allele carriers. These results suggest that TNF G308A polymorphism may be involved in the pathogenesis of periodontal disease in diabetics. Our study emphasizes the importance of considering genetic factors in the management of periodontal complications in diabetic individuals.

In a meta-analysis including the analysis of 31 studies, Ding et al. evaluated the potential effect of TNF-α G308A polymorphism on periodontitis. As a result, the AA genotype in Asians was associated with an increased risk for aggressive periodontitis [18]. On the other hand, a meta-analysis including the analysis of 52 studies suggested that the TNF-α G308A polymorphism could be a protective factor against chronic periodontitis and aggressive periodontitis in Asians [19]. In the meta-analysis by Shi et al. [16], TNF-α G308A polymorphism was associated with chronic periodontitis in T2DM patients in the Asian population, while no significant risk was detected among Caucasian populations [16]. In our study, we found a significant relationship between TNF-α G308A polymorphism and diabetic gingivitis, but we did not find a significant relationship between TNF-α rs1800629 polymorphism and diabetic chronic periodontitis.

Many previous publications have suggested that the A allele is a possible marker of the severity of periodontal disease and the authors attempted to explain this by the increased regulatory effect of the A allele on TNF-α production [16]. The result of our study suggests that the increase in the frequency of A allele may be an early indicator of the progression of periodontal disease in diabetic patients. Smoking is a major risk factor for periodontitis [20]. While actively smoking individuals were excluded from our study, those with a history of smoking were included. Environmental factors play an important role in the progression of periodontitis and smoking history may have masked the effect of this variation.

Brand et al. [21] investigated the effect of TNF G308A polymorphism on obesity in 176 Caucasian cases. TNF 308-A allele carriers were detected to have significantly higher BMI than the G allele carriers [21]. In our study, the frequency of A allele was found to be significantly higher in the diabetic gingivitis group. At the same time, BMI was higher in the diabetic gingivitis group compared to other groups. In light of these findings; the statistically significant increase in the frequency of TNF 308-A allele in the diabetic gingivitis group may be related to BMI rather than gingivitis. On the other hand, Modéer et al. investigated the periodontal status of obese adolescents. It was shown that more gingivitis and pathological periodontal pocket depth (>4mm) were present in obese patients compared to normal-weighted individuals, however there was no difference in incipient alveolar bone loss. So, the risk of gingivitis increases in obese patients. There is a positive correlation between obesity and periodontal risk indicators [22]. In our study, the A allele frequency was increased in the diabetic gingivitis group, it may be related to raising the risk of both obesity and gingivitis.

Periodontal disease arises from a complex interplay of factors, including genetic and epigenetic variations, lifestyle influences such as smoking and diet, systemic conditions like diabetes, and local dental or stochastic factors. Over 60 genetic variants have been implicated in periodontitis, highlighting pleiotropic links with conditions like cardiovascular diseases. Despite advances, further research is needed to deepen our understanding of how genetic and inflammatory pathways contribute to the disease's pathogenesis and to solidify cause-and-effect relationships [23]. On the other hand, a study in minipigs by Li et al. has shown that epigenetic changes, such as DNA methylation, contribute to increased susceptibility to periodontal disease in diabetic patients [24].

DM and periodontal diseases are common, chronic, multifactorial diseases. In many studies, diabetes was shown to be an important risk factor for the development of gingivitis and periodontitis [23]. Poorly controlled diabetes (A1c≥7) is associated with the progression of periodontal disease. In addition, periodontal diseases also adversely affect

glycemic control in diabetics [25]. Compatible with literature, blood glucose regulation was found to be worse in diabetics with periodontal disease in our study. A1c level was detected to be higher in the diabetic chronic periodontitis group (8.4%) than in the diabetic gingivitis group (7.5%). This finding indicates the adverse effect of poor glycemic control on periodontal tissues.

T2DM patients are known to have more gingival inflammation than non-diabetics [26]. PPD, CAL and PI levels are risk indicators for periodontal disease. In our study, the periodontal risk indicators of individuals with diabetic and non-diabetic periodontitis were examined. Mean PPD, CAL, and PI values were found to be higher in the group with diabetic periodontitis than in the non-diabetic periodontitis group, but this difference was not statistically significant.

Our study is the first in the literature, we examined the association between HIF-1α C1772T polymorphism and periodontal disease in diabetic patients. When we compared diabetic gingivitis and diabetic periodontitis groups with the non-diabetic periodontally healthy control group; no significant association was detected between the HIF-1α C1772T polymorphism and the development of periodontal diseases. In light of this information, we can emphasize that HIF-1α C1772T polymorphism does not play an important role in the development of diabetic periodontal disease. Nevertheless, the variation in this locus may have moderate effects on the development of periodontal diseases. However, environmental factors are dominant in both T2DM and periodontitis progression and may have caused this variation to be overlooked.

Our study had several limitations: (1) we had a small sample size, (2) it didn't include diabetic periodontal healthy individuals, and (3) the potential influence of demographic and clinical features, such as the duration of diabetes, presence of complications, and medications, on the development of periodontal disease could not be evaluated due to the limitations of our study design. This inability to perform subgroup comparisons among diabetes groups should be acknowledged as a limitation in interpreting the results.

CONCLUSION

TNF G308A polymorphism may be involved in the pathogenesis of periodontal disease in diabetics. Being a carrier of GA + AA, namely the presence of mutant A allele, increases the risk of diabetic gingivitis approximately 4-fold. To elucidate the importance of these SNPs in the pathogenesis of periodontal diseases, which occur more frequently in diabetes; more comprehensive studies, considering the effect of environmental factors that impact diabetes and periodontal diseases, should be conducted. Further research with larger cohorts and diverse populations is warranted to validate and expand upon these findings. Understanding the genetic underpinnings of periodontal disease in diabetic patients could pave the way for personalized therapeutic approaches and targeted interventions.

Author contribution

Study conception and design: SKK, YDİ, MA, RN, and TE; data collection: SKK, YDİ, NH, YÖ, AD, SD, RN, and TE; analysis and interpretation of results: SKK, SK, EK, MA, RN, and TE; draft manuscript preparation: SKK, MA, RN, and TE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Non-Interventional Clinical Research Ethics Board of Hacettepe University (Protocol no. GO 14/250 / 30.04.2014). Informed consent was obtained from each patient

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Astroviruses and celiac disease: a preliminary study into potential environmental triggers

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ABSTRACT

Objective: Celiac disease (CD) is a chronic, multi-organ, autoimmune disease in which different viruses may play a role in the pathogenesis. human astroviruses (*Mamastrovirus*) have also been shown to infect enterocytes and replicate in intestinal enteroids. Therefore, astroviruses are thought to be one of the critical environmental factors for celiac patients. This is the the first study investigating relationship between CD and astroviruses.

Materials and Methods: Previously-described PCR protocols for screening and typing of mamastroviruses were modified and optimized. These molecular methods were used for the stool and duodenal biopsy samples of 53 patients; six newly diagnosed CD, three celiac patients with good treatment responses, 23 refractory CD and 21 patients with dyspepsia.

Results: Astroviruses could not be detected in the stool and duodenal biopsy samples of 53 patients.

Conclusion: Although no evidence for the association of *Mamastrovirus* infection and CD could be demonstrated in this study, this might have been due to limited cohort size. Therefore, comprehensive studies with larger samples with different patient groups are needed.

Keywords: celiac disease, human astrovirus, *Mamastovirus*, Türkiye

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune/autoinflammatory disease with a lifelong gluten sensitivity of the small intestine. In the pathogenesis of CD, both innate and adaptive immune responses are stimulated by a mechanism that has not been fully elucidated. As a result of dysregulated immune response triggered by genetic and environmental factors, enterocytes of small intestine are damaged and malabsorption develops [1]. Viral infections are known to induce autoimmunity through different pathways and many autoimmune diseases are associated with viral infections [2,3]. Studies have shown that different viruses may also play role in the pathogenesis of celiac disease [2,4].

CD is a common disease affecting ~1% of most populations, and has an increasing prevalence observed in recent years [5,6]. The treatment for CD is based on the gluten free diet that restricts patient's life leading to uncompliance and suboptimal disease control. There is a need for better understanding the pathogenesis and developing novel treatment modalities. Not all genetic and environmental factors that influence the development and progression of the disease are recognized. Since a dysregulated immune response against gliadin causes damage to enterocytes, viruses have been investigated and shown to induce CD pathogenesis through molecular mimicry, immune activation, increased intestinal permeability and gut microbiome alterations [2,4,7-12]. Multiple studies have suggested that specific virus infections caused by *Rotavirus, Adenovirus, Reovirus,* and *Parechovirus* are linked to CD [7-12]. Although, viruses have been regarded to be one of the environmental factors that contribute to the disease's development, the mechanisms behind these relationships have remained unclear.

Mamastroviruses, one of the agents of viral gastroenteritis, have been reported to infect different tissues and organs other than the gastrointestinal tract and cause severe and systemic infections, especially in immunocompromised individuals [13]. They are non-enveloped, positive-sense, single-stranded RNA viruses have three genotypes/species were described; classic (HAstV-1–8, *Mamastrovirus hominis*), MLB (Melbourne) (MLB1-3, *Mamastrovirus melbournense*) and VA/HMO (Virginia/Human-Mink-Ovine-like) (VA1-5, *Mamastrovirus homustovis* and *Mamastrovirus virginiaense*) [14-20]. Although the capsid protein of astroviruses has the potential to damage the intestinal barrier, they do not induce clear pathology or cell death. There is little known about the mechanisms that influence the progression of mamastrovirus infections, hence it is unclear how other complications of infection, such as dysregulated secretion and malabsorption, emerge.

Experimental studies have demonstrated that mamastroviruses infect enterocytes and can replicate in intestinal enteroids, which are disease models generated by expanding patient-derived intestinal epithelial stem cells in 3D culture and used to study host-pathogen interactions [21]. If celiac patients' enterocytes are also infected with astroviruses, these viruses could be a initiating environmental factor in the pathogenesis of the disease by altering antigenic stimuli (via pathogen-recognizing molecular patterns (PAMP)), cytokine composition, and/or immune response in the microbiota. Mamastroviruses may be one of the critical environmental factors for celiac patients. This is a preliminary study aiming to determine whether there is a link between celiac disease and the presence of mamastroviruses.

MATERIALS AND METHODS

Sampling

The study was designed as a prospective cross sectional study, and was approved by the Hacettepe University Non-Invasive Clinical Research Ethics Committee (No: 2020/20-29 and 2021/13-125).

The study included four groups; namely patients with newly diagnosed CD, good treatment responsive CD, inadequate treatment response, and dyspepsia who were on follow up at Gastroenterology Clinic in Hacettepe University Hospital between April 2021 and March 2023. The duodenal biopsies and stool samples were collected and tested for the presence of astroviruses via reverse-transcription PCR (RT-PCR).

Nucleic acid isolation and screening

Nucleic acids were extracted from duodenal biopsies and stool samples using NucleoSpin RNA virus kit (Macherey-Nagel, Germany). RNA was reverse transcribed with random hexamers using the instructions of manufacturer (A.B.T. cDNA Synthesis Kit with RNAse Inhibitor (C03-01-20), A.B.T Laboratory Industry, Türkiye).

The 430base pair (bp) sequence in the RNA-dependent RNA polymerase encoding region was amplified via the semi-nested PCR. The primers provided by Japhet et al. and Finkbeiner et al. were revised and used in this study (Table 1) [18,22].

Each reaction mixture contained 2 mM $MgCl_2$, 0.3 mM dNTPs, 10 pmol of primers, and 0.75 U Taq DNA polymerase (A.B.T Laboratory Industry, Türkiye) in 30 µL volume. Thermal cycling parameters for the first round were as follows: an initial denaturation at 94°C for 5 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 51°C for 1 min, extension at 72°C for 1 min and the final extension step of 72°C for 3 min. An initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30s, annealing at 53°C for 30 s, extension at 72°C for 1 min, and a final extension step of 72°C for 3 min for the second round. PCR products were visualized by electrophoresis on 1.5% agarose gels.

The methods were validated using stool sample from a patient infected with *Mamastrovirus* infection. The sample was used in each extraction process, whereas isolated RNA was used in each reverse transcription and PCR run.

Mamastrovirus typing

Different PCR protocols were applied for the typing of mamastroviruses as classical (*Mamastrovirus hominis*), MLB (*Mamastrovirus melbournense*) and VA/HMO (*Mamastrovirus homustovis* and *Mamastrovirus virginiaense*). Each reaction mixture contained 2 mM $MgCl_2$, 0.3 mM dNTPs, 10 pmol of primers (Table 2), and 0.75 U Taq DNA polymerase (A.B.T Laboratory Industry, Türkiye) in 30 µL volume. Thermal cycling parameters were indicated below for each type and PCR products were visualized by electrophoresis on 1.5% agarose gels.

Table 1. Primers used for the screening of samples

Primers	Polarity	Sequence	Reference
AV93 (s)-1	Sense	GAYTGGACICGNTWTGATGG	Revised from Japhet et al. [22]
AV91 (as)-1	Antisense	TTTGGTCCDCCCCTCCA	Revised from Japhet et al. [22]
SF0076 (as)	Antisense	CWGGYTTDACCCACATNCC	Revised from Finkbeiner et al. [18]

Table 2. Primers used for the typing of astroviruses

Type	Primer	Polarity	Sequence	Reference
Classical (*Mamastrovirus hominis*)	Mon269-1	Sense	CAACTCAGGAAACARGGTGT	Revised from Finkbeiner et al. [18]
	AstVcR	Antisense	GCATANCCTGTRAANCACCA	This study
MLB (*Mamastrovirus melbournense*)	SF0053	Sense	CTGTAGCTCGTGTTAGTCTTAACA	Finkbeiner et al. [18]
	SF0061-1	Antisense	GTTCATTRGCACCATCAGARC	Revised from Finkbeiner et al. [18]
VA/HMO (*Mamastrovirus homustovis* and *Mamastrovirus virginiaense*)	SF0178-1	Sense	GCTGTMACCGTCTCTGCCACCAT	Revised from Finkbeiner et al. [18]
	SF0179-1	Antisense	CATGCTGCATCCTTGTAGGTAGA	Revised from Finkbeiner et al. [18]

Classical mamastroviruses (*Mamastrovirus hominis*); an initial denaturation at 94°C for 5 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 53°C for 45 s, extension at 72°C for 1 min and the final extension step of 72°C for 3 min. Product size is 575 bp.

MLB mamastroviruses (*Mamastrovirus melbournense*); an initial denaturation at 94°C for 5 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 56°C for 30 s, extension at 72°C for 1 min and the final extension step of 72°C for 3 min. Product size is 402 bp.

VA/HMO mamastroviruses (*Mamastrovirus homustovis* and *Mamastrovirus virginiaense*); an initial denaturation at 94°C for 5 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 1 min and the final extension step of 72°C for 3 min. Product size is 475 bp.

RESULTS

Demographic characteristics of the patients

The duodenal biopsies and stool samples of 53 patients were included in this study. There were six patients with newly diagnosed CD, three CD patients with well treatment response and 23 CD patients with inadequate treatment response, and 21 patients with dyspepsia. Thirty four of the patients (64%) were women, and 19 (36%) of them were men. The mean age was 39 years.

Molecular screening and typing of samples

Protocols for screening and typing of samples were optimized using a positive control samples (Figure 1 and 2). We screened duodenal biopsies and stool samples belonging to 53 patients, however mamastroviruses were not detected in these samples (Figure 3).

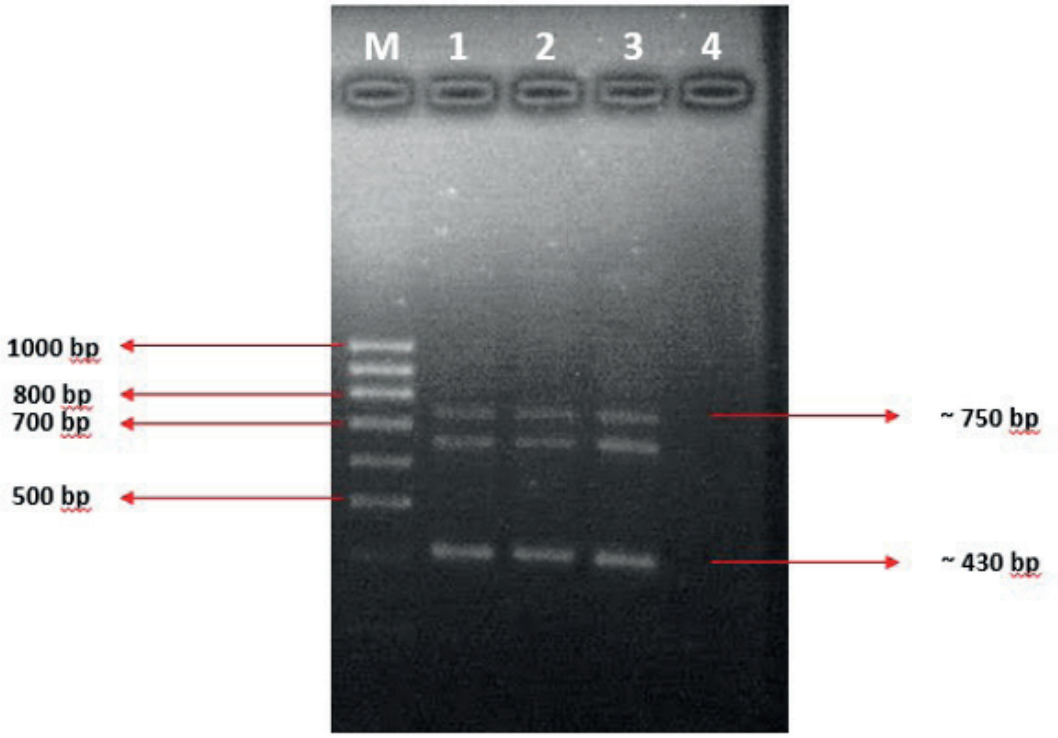

Figure 1. Optimization results of semi-nested PCR protocol used for screening. The bands belong to the positive control. The expected product size is 750 bp for RT-PCR and ~430 bp for semi-nested PCR. Wells 1, 2 and 3 belong to the positive control, whereas well 4 belongs to the negative control. M: Marker (100-1000 bp).

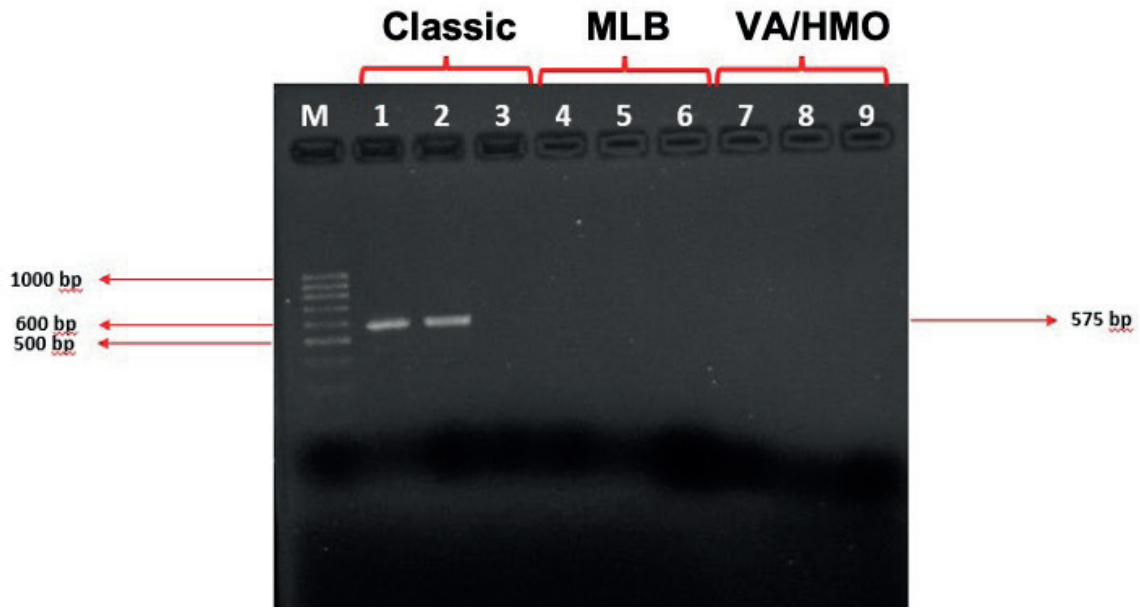

Figure 2. Optimization results of PCR protocols used for typing. The bands belong to the positive control. Wells 1 and 2 are the classic astroviruses (HAstV-1–8, *Mamastrovirus hominis*) (575 bp) and well 3 is the negative control. Wells 4 and 5 are the PCR result specific for the MLB astroviruses (MLB1-3, *Mamastrovirus melbournense*) (402 bp) and well 6 is the negative control. Wells 7 and 8 are VA/HMO astroviruses (VA1-5, *Mamastrovirus homustovis* and *Mamastrovirus virginiaense*) specific PCR result (475 bp) and well 9 is negative control. M: Marker (100-1000 bp).

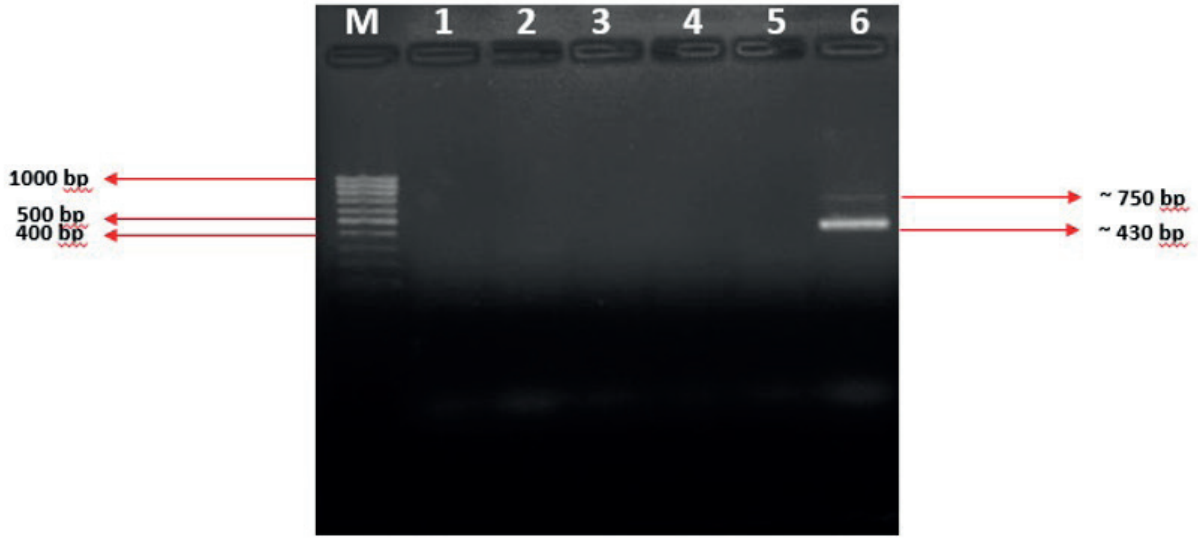

Figure 3. Screening PCR results of patient samples. Wells 1, 2, 3 and 4 are patient samples, well 5 is negative control and well 6 is positive control. M: Marker (100-1000 bp).

DISCUSSION

CD is a multisystemic disease characterized by enterocyte damage caused by gluten consumption and the development of specific antibodies. Several studies have established a link between various enteric viruses and the pathogenesis of celiac disease [4,8-12]. However, the relationship between mamastroviruses, which are known to cause gastroenteritis—particularly in immunocompromised individuals and children—and celiac disease remains largely unexplored [23,24]. Additionally, there is limited information regarding the prevalence of mamastroviruses in Turkey [24]. This study aims to serve as a preliminary investigation into whether there is an association between CD and the presence of mamastroviruses.

Stool and duodenal biopsy samples of 53 patients, including newly diagnosed celiac disease patients, celiac patients with good and inadequate response

to treatment and dyspepsia patients, were screened using PCR-based methods but no evidence for mamastroviruses were documented.

It is important to note that the study faced particular limitations that may have influenced the results. Primary limitation was the sample size, which may not have been large enough to detect low-frequency viral infections. The study was conducted during the COVID-19 pandemic, many of the follow-up patients postponed their follow-up visits, making it unable to reach the targeted patient population in each group. It is possible that larger, more comprehensive studies with a greater number of patients—particularly those representing various stages of CD, including those with different treatment responses—would yield different results.

The study did not find any mamastroviruses in the patient samples while it is important to acknowledge that the pathogenesis of CD is multifactorial. Although viral infections, including mamastroviruses, could potentially act as environmental triggers, the immune response to gluten and the genetic predisposition of individuals remain the primary drivers of the disease.

In conclusion, while our findings do not support a direct link between mamastroviruses and celiac disease, they underscore the need for further research to explore the complex interactions between viral infections and autoimmune disorders like CD. To definitively clarify whether mamastroviruses play a role in the pathogenesis of CD, future studies should aim to include larger and more diverse patient populations, encompassing a broader range of CD subtypes.

Author contribution

Study conception and design: CP, HYB, and KE; data collection: CP, TŞ, CŞ, İET, Sİ, CS, and HŞ; analysis and interpretation of results: CP, TŞ, and İET; draft manuscript preparation: CP, HYB, and KE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Invasive Clinical Research Ethics Committee (Protocol no. 2020/20-29 and 2021/13-125).

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Facial zona zoster following cryotherapy in an immunocompetent patient

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ABSTRACT

Cryotherapy is commonly used in different medical fields including dermatology, urology, oncology and sports medicine. The well-known complications of cryotherapy include dyspigmentation, scar formation and hair loss. Herein, a facial zona zoster case is reported as an unexpected complication of cryotherapy.

Keywords: cryotherapy, herpes zoster, virus diseases.

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INTRODUCTION

Cryotherapy is a non-invasive procedure which is commonly used in dermatology to treat various benign and malignant skin conditions including warts, seborrheic keratoses, skin tags, actinic keratoses, superficial basal cell carcinomas, etc. Liquid nitrogen is typically used to cool the intended tissue to create ischemic necrosis and form ice crystals [1]. Herein, an unusual case of zona zoster following crytotherapy applied for solar lentigines and seborrheic keratoses, is reported.

CASE PRESENTATION

A 71-year old man was seen at the dermatology outpatient clinic due to the gradually increasing number of brownish skin lesions involving the face and scalp. After clinic examination, he was diagnosed with multiple solar lentigines, seborrheic keratoses and actinic keratoses. The dermatoscopy supported the clinical diagnoses. He did not have any other systemic disease and was not using any kind of medication. Strict use of sunscreen was recommended to the patient and biweekly cryotherapy application was started. Two days after the fifth cryotherapy session, the patient developed mildly-painful, pruritus erythematous plaques involving the right mandibular area, inferior cheek, scalp and ear compatible with dermatomal distribution (mandibular division of trigeminal nerve, cervical 2-4 nerves) (Figure 1). The final diagnosis was zona zoster; the patient didn't have any other recent provoking factor such as infection, surgery, distress or immunosuppression. Additionally, he wasn't previously diagnosed with zona before and he remembered having chickenpox disease during childhood. Oral brivudine treatment for a week resulted in the crusting of the lesions even though mild burning sensation seemed to persist.

DISCUSSION

Zona zoster is an infectious skin disease characterized by sudden onset of painful vesicular eruption typically involving one or more dermatomes of the skin. Some well-known risk factors for zona development are immunosuppression, malignancy, older age, female gender and psychological stress [2]. Even though physical trauma is a less-defined contributing factor, there are a few reports in the literature related to the development of zona after botulinum toxin mixed with hyaluronic acid injection [3] and thoracic trauma [4]. Our patient didn't have any other comorbidities or immunosuppression

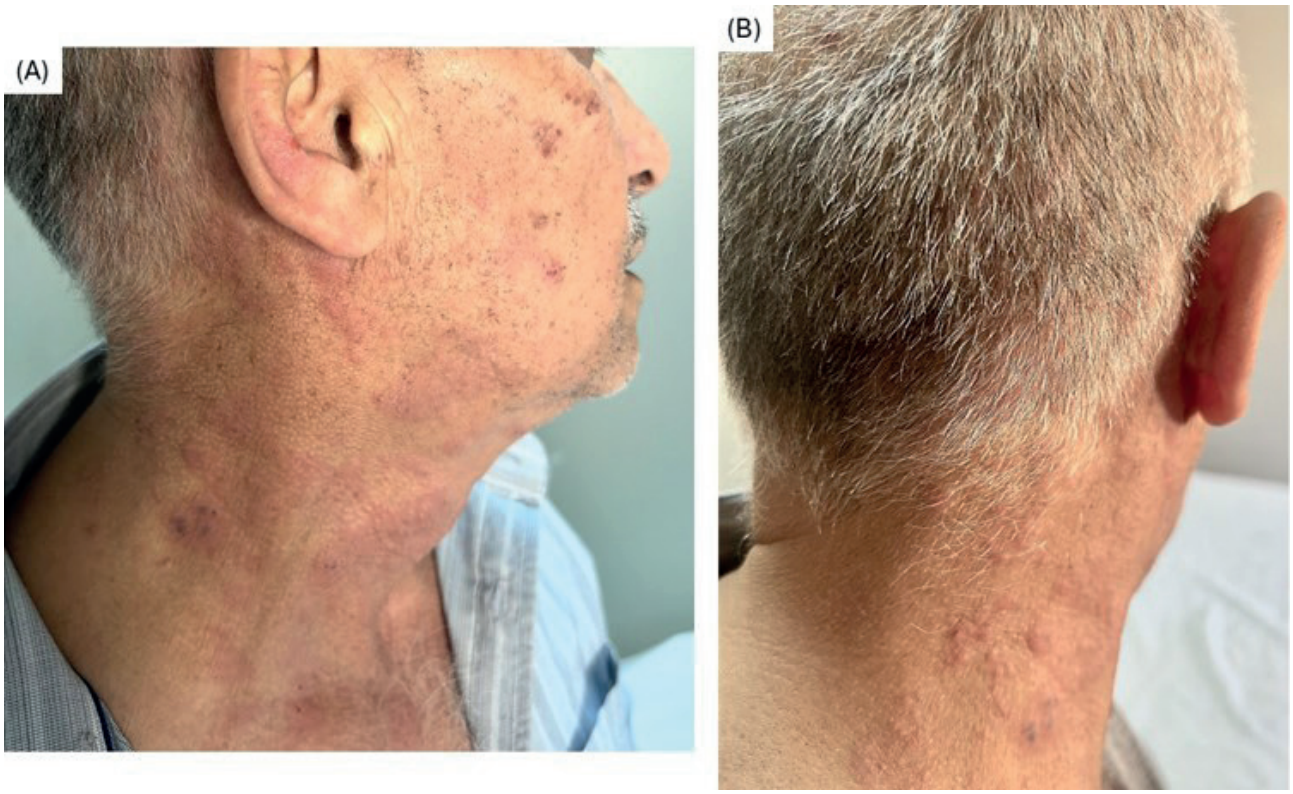

Figure 1. Erythematous plaques involving the right mandibular area, inferior cheek and neck (A) and posterior scalp (B).

which would play a role in the emergence of zona zoster. He developed erythematous papules and plaques involving the right mandibular area and scalp which were all compatible with the sites of previous cryotherapy application for solar lentigines and seborrheic keratoses. Similar to our case, Lee and Ryman [5] reported a case of herpes zoster observed in the right forehead of 56-year old man after cryotherapy treatment for solar keratoses. Trauma-induced viral activation might have played a role in the development of zona in our present case. To prevent the complications associated with zona zoster in eldery individuals, two doses of recombinant zoster vaccine is recommended by Center for Disease Control and Prevention for people who are at age 50 years or older [6].

All in all, it is important to emphasize that cryotherapy could be a provoking factor for the develolopment of zona in otherwise immunocompetent individuals.

Author contribution

Study conception and design: EB; data collection: EB; analysis and interpretation of results: EB; draft manuscript preparation: EB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Since a single case is reported, no ethical approval is needed.

Funding

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

The conus artery as a lethee in coronary artery disease

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ABSTRACT

Collaterals connecting coronary arteries may protect the heart from ischemic attacks, thus mediate in the preservation of myocardial functions. Symptoms and ventricular functions are closely related to the quality of coronary collaterals. In the presence of chronic total occlusion (CTO) in the left anterior descending artery (LAD), collateral circulation from the conus artery to the LAD is rare but may be life-saving. We report a 44-year-old patient with moderate left ventricular dysfunction and multi-vessel coronary disease in whom collateral flow was supplied by the conus artery, connecting to distal to the LAD CTO.

Keywords: collateral, conus artery, myocardial function.

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INTRODUCTION

Coronary collaterals are blood vessels that provide connections between coronary arteries. It may protect the heart from ischemic attacks, thus resulting in preserved myocardial functions. The better developed the coronary collaterals, the better the myocardial protection [1-3]. The most commonly observed coronary collaterals are connections between the septals of the left anterior descending artery (LAD) and the posterior descending artery (PDA) of the right coronary artery (RCA). The collateral pattern formed by the conus artery has a low incidence and should not be overlooked [4]. Here, we present a young patient with moderate left ventricular dysfunction and multi-vessel coronary disease in whom collateral flow was supplied by the conus artery, connecting to distal to the lesion with complete occlusion of the LAD.

CASE PRESENTATION

A 44-year-old man with shortness of breath and inability to lie flat (orthopnea) was admitted to the cardiology clinic with decompensated heart failure. The patient had risk factors of smoking, hypertension and hyperlipidemia and had a history of hospitalization for decompensated heart failure in another hospital about 5 months ago. On physical examination, blood pressure was 140/90 mmHg, pulse rate: 110 beats/min and decreased respiratory sounds and rales were heard in the basal parts of the lungs. Other physical examination findings were within normal limits. Electrocardiography showed sinus tachycardia and echocardiography showed global hypokinesia with an ejection fraction (EF) of 40%. After stabilization with guideline-based treatment, coronary angiography was performed. Coronary angiography showed a 90% stenosis in the LAD proximally and a chronic total occlusion (CTO) lesion immediately afterwards (Figure 1). No major lesion was observed in the circumflex artery. Right coronary angiography showed 90% stenosis in the middle part of the RCA and 99% stenosis in the middle segment of the well-developed acute marginal branch of the RCA. The conus artery was seen to arise from the RCA ostium and to meander anterior to the pulmonary artery and to merge just distal to the LAD CTO lesion, supplying the middle and distal segments of the LAD. Additionally, there was a severe stenosis (95%) in the proximal part of the conus artery (Figure 2). After successful coronary by-pass surgery carried out due to both multi-vessel disease involving the LAD and low

EF, the patient was discharged uneventfully. On examination 3 months later, we observed that the general condition of the patient was good and his EF increased to 50%.

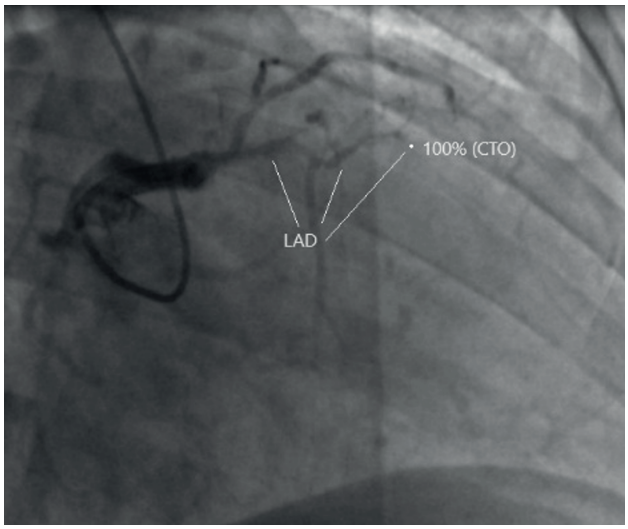

Figure 1. Coronary angiography shows a chronic total occlusion (CTO) lesion in the left anterior descending artery (LAD).

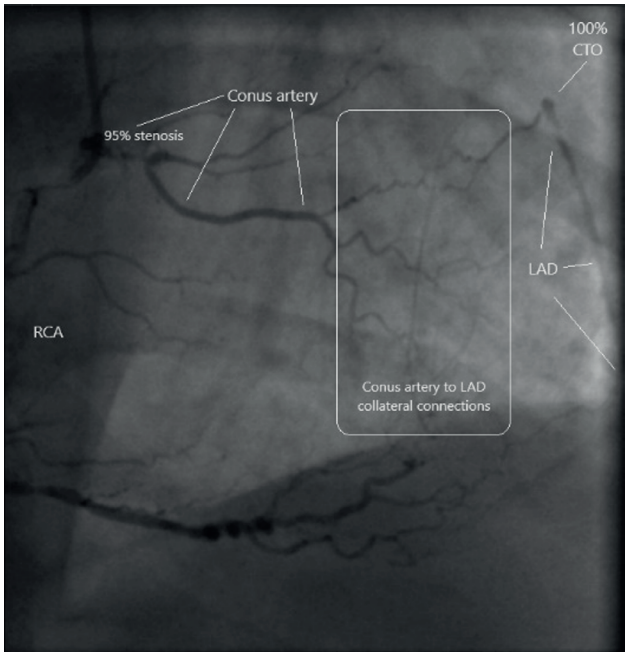

Figure 2. Right coronary angiography shows collateral circulation from the conus artery, branching from the ostium of the right coronary artery (RCA), to distal to the chronic total occlusion (CTO) in the left anterior descending artery (LAD).

DISCUSSION

The present case is valuable as a reminder of the importance of defining the presence, origin and course of coronary collateral flow in a CTO lesion. Our case had a conus artery branch providing collateral connections between proximal RCA and distal to LAD CTO lesion.

The collaterals may play an active role in maintaining myocardial viability, and the well-developed collaterals are known to improve cellular function and global myocardial performance in CTOs [1-3]. Moreover, they may bridge over in protect the myocardium from ischemia during episodes of coronary ischemia and prolong the chance of intervention in the limited time from the onset of acute myocardial infarction to successful coronary reperfusion [1,2,4,5].

It should be determined from which vessel (from where) the collateral blood flow to the chronically occluded vessel is provided. McEntegart et al. [4] evaluated collateral circulation to chronically occluded coronary arteries, and they reported that collateral blood flow to the LAD originated from the PDA in 52.3%, from the RV in 26.8% and from the conus branch in 5.9% of 159 cases of LAD CTO. The conus artery supplies blood flow to the conus or outflow tract of the right ventricle. It may arise from the first segment of the RCA or from the superior and anterior to the ostium of RCA as a separate branch directly from the aorta [6-8]. In the present case, we identified the conus artery branch stemming from the RCA ostium as the collateral vessel providing blood supply to distal to the LAD CTO lesion.

Detailed identification of the coronary collateral is important not only for diagnosis but also for treatment. The detection of such a collateral vessel may influence the treatment decision in favour of PCI in CTO lesions for several reasons. First, the conus artery providing collateral blood flow to the true lumen distal to the CTO lesion allow clear

visualisation of the distal vascular bed. Therefore, this connection can be used for microcatheter tip selective injection facilitating antegrade approach and as a collateral channel for retrograde approach in all CTO PCI. Second, it can be used as a vessel for wire / balloon anchoring to fix and increase support for RCA guiding catheter in RCA CTO PCI. Coronary surgery should be considered for the treatment of patients who cannot be treated with PCI in LAD CTO [9]. Our case had a low left venticular ejection fraction. He also had multivessel disease involving LAD, and a thin, tortuous and diseased conus artery providing connection between RCA and LAD, as shown in Figure 1 and 2. For these reasons, our patient underwent successful coronary artery by-pass operation. In patients undergoing coronary surgery, the origin and course of the conus artery should be well known to avoid intraoperative injury. The conus artery may be damaged during surgical interventions involving right infundibulum manipulations, especially in the case of its intramyocardial course [7,8]. Levin et al. reported that the conus artery could not be demonstrated angiographically in almost 20% of cases [8]. When conventional angiographic methods are failed to demonstrate coronary collateral flow, especially in cases where surgical procedure or CTO PCI is planned, multidetector coronary computed tomography (MDCT) should be considered [6-8].

Coronary collateral circulation is an important factor in the pathophysiology of coronary disease. Symptoms and prognosis in patients with coronary artery disease depend on the quality of the collateral circulation. If the collateral vessel is weak and/or diseased, ventricular function may not be adequately preserved [1-4]. Shokry et al. [3] recently showed that the presence of well-developed coronary collateral could independently predict with high accuracy myocardial viability. In our case, the conus artery branching from the RCA had both a thin and tortuous structure and severe atherosclerotic stenosis. We think that the reason for the moderate decrease in ventricular function observed in our case was both the underlying multi-vessel disease and the diseased conus artery supplying collateral flow to distal to the LAD CTO lesion.

In conclusion, coronary collateral flow is of paramount because it can reduce the severity of ischemic attacks and thus contribute to the preservation of myocardial functions. In CTO lesions, if present, the origin and course of the collateral vessel supplying blood flow to the distal part of the lesion should be described in detail. If uncertainty, MDCT should be performed, especially in patients in whom CTO PCI or surgical procedure is planned. Conus branch artery providing collateral connections between two different vascular zone presents a few technical opportunities, including selective contrast injection, anchoring, and vascular channel (collateral) for retrograde approach, to increase the success of and/or to simplify the PCI in CTO lesions. In patients undergoing coronary surgery, the conus artery providing collateral flow should not be damaged during the procedure.

Author contribution

Study conception and design: MY; data collection: MY and ZD; analysis and interpretation of results: MY and ZD; draft manuscript preparation: MY and ZD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Informed consent was obtained from the patient for participation and publication.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Leptomeningeal carcinomatosis: a rare phenomenon in neurology?

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ABSTRACT

Leptomeningeal involvement may be caused by various conditions, and patients may present with different clinical findings. The causes of this condition may be carcinogenic, infectious, inflammatory and autoimmmunity. The prognosis is dependent upon the underlying cause.

We present three cases of leptomeningeal involvement with different diagnoses and clinical findings.

Keywords: leptomeningeal involvement, leptomeningeal carcinomatosis, rheumatoid arthritis, neuroendocrine tumour, magnetic resonance imaging

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INTRODUCTION

The leptomeninges contain the arachnoid and pia layers, and the pachymeninges contain the dura. Leptomeningeal carcinomatosis (LC) is the infiltration of the cerebrospinal fluid and the leptomeninges of the brain and spinal cord with tumour cells [1-3]. Leptomeningeal metastasis (LM) is seen in 4-15% of solid tumours. It is the first sign of metastasis in 10% of cases [1]. Rarely, primary involvement of the leptomeninges has also been reported in diseases such as lymphoma, glioma, melanocytosis and amyloidosis. In addition, the leptomeninges may be affected by autoreactive T-cell traffic in autoimmune diseases such as systemic lupus erythematosus (SLE), sarcoidosis and rheumatoid arthritis (RA) [1,2]. Patients may present with headache, vomiting, cranial nerve deficits, seizures, loss of strength and sensation, gait abnormalities, incontinence and hydrocephalus [2,3]. Contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology are important in the diagnosis [2,3].

In this study, we aimed to discuss three cases with different diagnoses and different clinics in which leptomeningeal involvement was found in the light of the literature. Written informed consent was obtained from patients for publication of this case report and any accompanying images.

CASE-1

A 53-year-old man presented with complaints of stuttering in his speech and involuntary movements in his right arm and leg for one month. On neurological examination, the patient was observed to be cooperative and oriented. Cranial nerve examination was normal, cerebellar tests on the right were unsuccessful, and tandem gait was impaired. Additionally, myoclonic jerks were present on the right. Electroencephalogram showed bifrontal epileptiform activity. Contrast-enhanced cranial MRI showed left parietal leptomeningeal involvement (Figure 1). No significant pathology was found on direct examination, biochemistry, culture, and cytology of CSF. Blood tests for vasculitis showed elevated levels of C-reactive protein at 25mg/dL (<5mg/dL), rheumatoid factor at 128.7 IU/mL (<20IU/mL), and anti-cyclic citrullinated peptide at >500 IU/mL(<15IU/mL). Tumour markers were negative. Following rheumatology consultation, the patient was diagnosed with rheumatoid arthritis. Valproic acid 2x500 mg and intravenous methylprednisolone (1000 mg/day) were added to the treatment for myoclonies for 7 days. Follow-up treatment was planned with oral methotrexate tablet (15 mg/week), methylprednisolone (4 mg/day) and valproic acid (2x500 mg). After this treatment he had no active complaints.

CASE-2

A 49-year-old man with no known chronic disease, presented with a generalised tonic-clonic seizure. The patient had a 4-month history of progressive girdle pain and gait disturbance. He had been bedridden for 2 months, had double vision and hoarseness for 1 month. On neurological examination, the patient was observed to be cooperative and oriented. Cranial nerve examination was normal, while motor system examination revealed muscle strength of 4/5 in all extremities. Deep tendon reflexes (DTR) were globally absent. Lumbar MRI showed multiple bone metastases and contrast-enhanced brain MRI showed leptomeningeal involvement (Figure 2). Lumbar puncture revealed that the protein level was 242mg/dL (15-45 mg/dL), the glucose level was 46,2 mg/dL in the CSF, no cells were found. No significant pathology was found in CSF culture and cytology results. Intravenous methylprednisolone (1000 mg/day) and levetiracetam (2x500 mg) were administered. The bone marrow biopsy, performed as a screening for malignancy, was consistent with a small cell neuroendocrine tumour. The patient who was planned to be referred to medical oncology for chemotherapy, was referred to intensive care unit due to his poor general condition. He died two months after admission to the hospital.

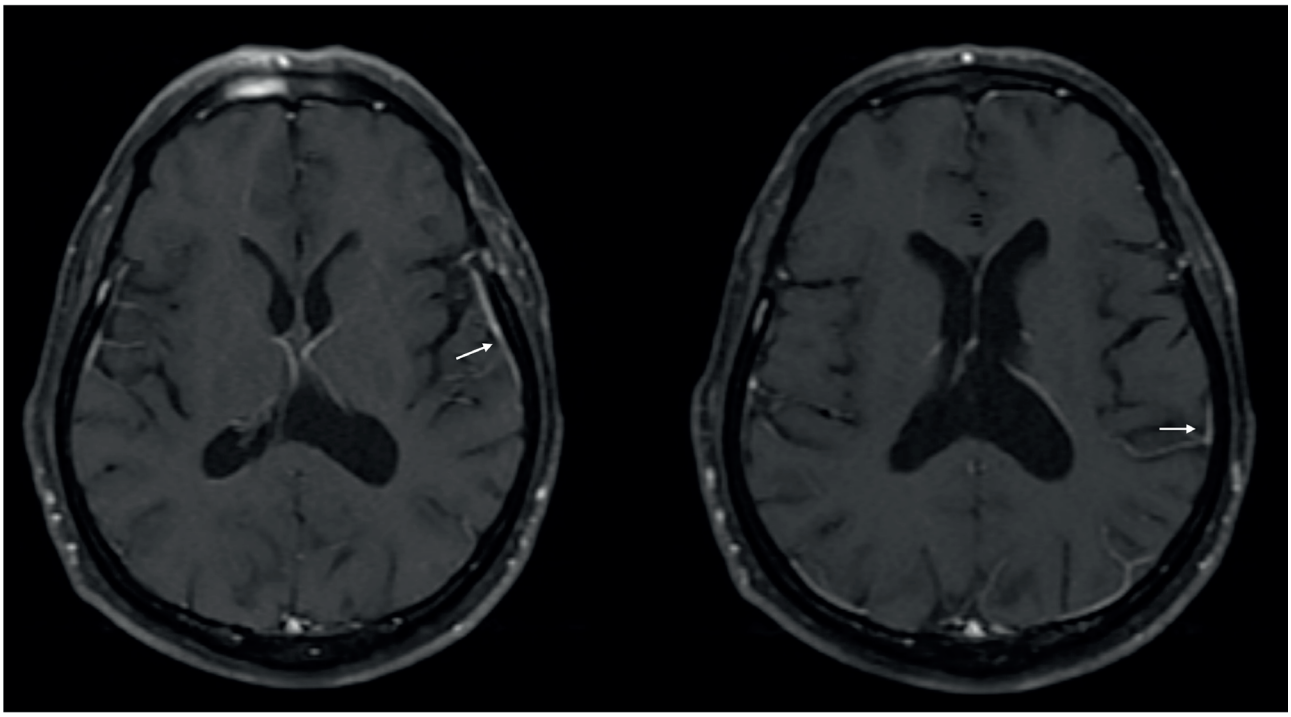

Figure 1. Case-1. Contrast-enhanced MRI of brain. Contrast-enhanced T1-weighted axial image. Showed left parietal leptomeningeal involvement (white arrow).

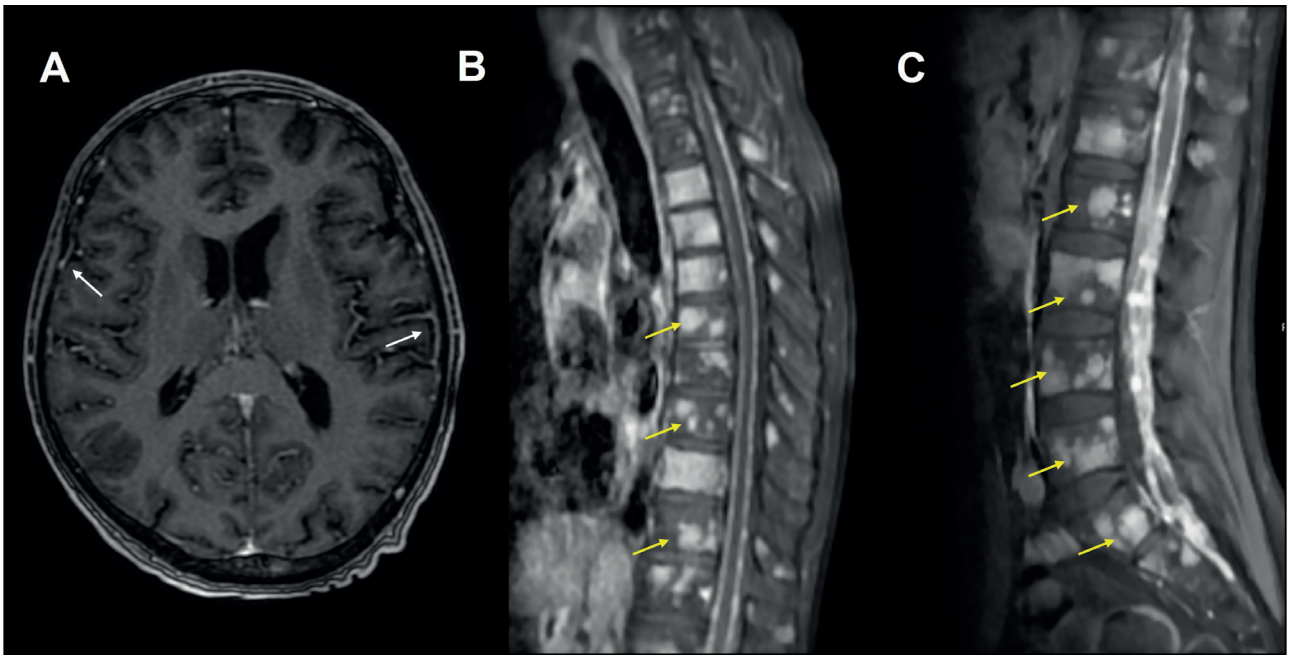

Figure 2. Case-2. (A) Contrast-enhanced MRI of brain. Contrast-enhanced T1-weighted axial image. Showed leptomeningeal involvement (white arrow). (B) Contrast-enhanced thoracic spine MRI. T1-weighted sagittal image (yellow arrow). (C) Contrast-enhanced lumber spine MRI. T1-weighted sagittal image. Showed multiple bone metastases (yellow arrow).

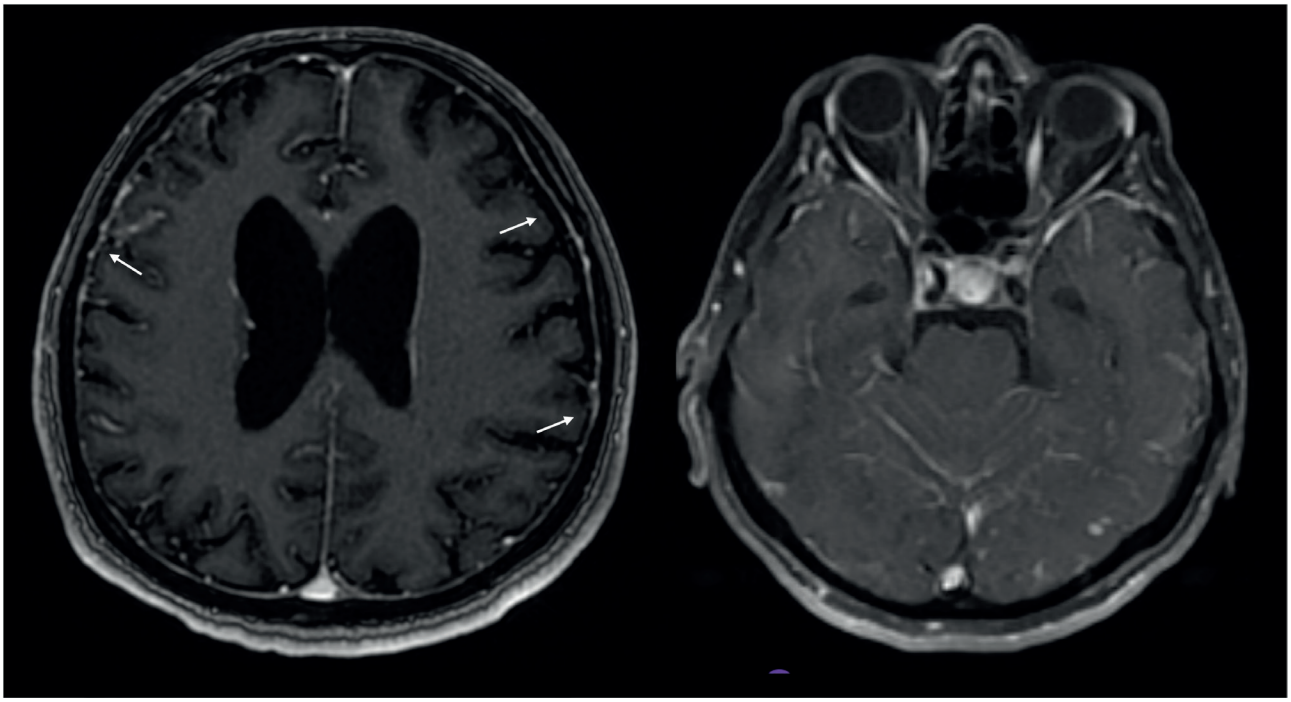

Figure 3. Case-3. Contrast-enhanced MRI of brain. Contrast-enhanced T1-weighted axial image. Showed leptomeningeal involvement (white arrow).

CASE-3

A 72-year-old male patient presented with complaints of slurred speech and difficulty walking, which developed following diarrhea and lasted for ten days. During the neurological examination, the patient was conscious, cooperative, and oriented. The patient had dysarthric speech, paralysis of the sixth cranial nerve on the right and paralysis of the central facial nerve on the left. The patient's gait was ataxic and DTR were hyperactive. The patient was diagnosed with pancreatic cancer a year ago,

and metastases in the liver and lungs were later detected on CT scans. Whole body Positron Emission Tomography-Computed Tomography (PET-CT) imaging revealed diffuse metastatic findings throughout the body, and the contrast-enhanced brain MRI showed leptomeningeal involvement (Figure 3). There was a rapid deterioration in the patient's general condition and he died within a week.

DISCUSSION

The leptomeninges, the cerebrospinal-fluid-filled tissues surrounding the central nervous system, play host to various pathologies including infection, neuroinflammation, autoimmune disease and malignancy [4,5]. Patients may present with a variety of clinical symptoms and the prognosis depends on the cause of the leptomeningeal involvement. Carcinomatous meningitis, also known LM or LC, is a rare complication of advanced cancer that occurs when the disease spreads to the meninges surrounding the brain and spinal cord, often from neoplastic causes or, less commonly, from infectious causes that disrupt the blood-brain barrier [3].

In autoimmune diseases such as SLE, sarcoidosis and RA, it is important to consider leptomeningeal involvement as a potential differential diagnosis [1,2]. Although CNS involvement is observed in SLE, aseptic leptomeningeal involvement has been reported very rarely with a rate of 1.4-2% [6,7]. This may be due to increased inflammatory molecules resulting from autoimmune pathology and dysregulation in the clearance of immune complexes [8]. Rheumatoid meningitis may present with seizures resistant to antiepileptic treatment, recurrent stroke-like episodes, or aseptic meningitis with headache, fever, and altered consciousness [9,10].

The 5-year survival rate for pancreatic cancer is less than 5%. CNS and leptomeningeal involvement are rare, occurring at a rate of 0.3%, and prognosis is worse in these cases [9,11]. Neuroendocrine tumors (NETs) are a group of heterogeneous malignancies of epithelial or neural origin, with a range of histologies including low-grade carcinoid, intermediate-grade atypical carcinoid, and high-grade small cell neuroendocrine carcinoma. Small cell neuroendocrine carcinomas (SCNC) are highly aggressive and have a high recurrence rate [12]. Leptomeningeal involvement is reported as case reports in poorly differentiated NETs [13-16].

Our cases were leptomeningeal involvements with different diagnoses. Two cases were carcinomatous and one case was inflammatory. Clinical findings were widely described, including headache, speech disorder, cranial nerve findings, epileptic seizures, paresis, ataxia, and urinary incontinence [2,3]. Different clinical patterns were also observed in our cases.

CSF have an important role in the diagnosis [17]. When investigating CSF, it is important to examine cell count, pressure, protein and glucose levels, as well as perform cytological and immunohistochemical examinations and tumor marker tests [17]. Our second case showed a significant elevation in CSF protein, which is consistent with findings in the literature. The first case with leptomeningeal involvement of RA had normal CSF protein. The third case with pancreatic cancer, lung metastasis and LC could not be lumbar punctured due to rapid deterioration. It is important to note that malignant cells can be detected in the initial CSF cytology in only 50% of LC cases [18]. Therefore, repeat lumbar puncture is recommended. In addition, elevated protein level and decreased glucose level in CSF may also help in diagnosis [19]. Studies have reported that tumor markers in CSF can be detected earlier than radiological findings and are more diagnostic than those in serum.

MRI and CT are important radiologic imaging techniques for the diagnosis, prognosis, and survival of LM. Although contrast-enhanced imaging is more sensitive than cytological examination, it is not specific [17]. Studies have shown that contrast-enhanced T1-weighted sequences in MRI are more sensitive in the detection of LM [20]. In our cases, leptomeningeal contrast enhancement was also observed in MRI with contrast-enhanced T1 sequence.

The prognosis for patients with LC is poor, with limited survival of 1-4 months [1,2]. Palliative treatment options have been used to prolong survival to six months, but there have also been reports of protection against further neurological deficits [21]. It has been reported that

leptomeningeal involvement due to autoimmune causes has a better response to treatment [21]. In the Apostolidis et al. series the mean duration of survey in patients with LC was reported to be ten months [22]. In our cases, the first patient had complaints for one month, the second patient had complaints for four months, and the third patient had a diagnosis of pancreatic cancer one year ago, and a ten-day history of clinical deterioration. The second patient died two months after hospitalization, and the third patient died one week after hospitalization due to rapid progression.

In conclusion, leptomeningeal involvement resulting from disruption of the blood-brain barrier may occur as a result of malignancy, infection, autoimmune causes such as SLE, sarcoidosis, and RA. It causes a wide variety of symptoms depending on the site of involvement of the leptomeninges; therefore, clinical presentation of patients may vary. CSF examination and radiological imaging, especially MRI, play important roles in diagnosis. The prognosis of LC is poor and aggressive and palliative treatment options are used; rheumatological and infectious causes have a better prognosis. In cases with multisystemic and different neurological symptoms, leptomeningeal involvement should be kept in mind.

The limitation of this study is that it included 3 cases of leptomeningeal involvement due to solid tumor, neuroendocrine tumor and rheumatoid arthritis. This subject needs to be reviewed with larger case series or meta-analyses including multiple studies.

Author contribution

Study conception and design: BGB, ES, and SK; data collection: BGB, BCOK, PB, ES, and SK; analysis and interpretation of results: BGB, ES, BCOK, PB, SK, MGŞ, and MFÖ; draft manuscript preparation: BGB, ES, BCOK, PB, SK, MGŞ, and MFÖ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The informed consent was obtained from the patient for the participation and publication.

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Conflict of interest

The authors declare that there is no conflict of interest.

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