Consideration of serum IL-36α and β levels trends in two patients with chikungunya fever

Makoto Kondo[1], Yoshiaki Matsushima[2], Takehisa Nakanishi[2], Shohei Iida[2], Koji Habe[2], and Keiichi Yamanaka[2]

[1]Mie University
[2]Mie Univ

April 3, 2023

1. Introduction

Chikungunya fever is a persistent joint pain disease caused by mosquito-borne arboviruses: chikungunya virus (CHIKV). In Chikungunya fever, inflammatory cytokines such as IL-6, Il-17, IL-22, and IL-23 [1,2] are involved in chronic joint pain, but there are no reports on whether IL-36 is specified as a cause of joint pain. This case study compares the changes in IL-36α and β levels during infected chikungunya fever and the recovery. This article highlights the relationship between chikungunya fever and IL-36.

2. Case Presentation

We previously reported two cases with chikungunya fever after traveling to Cook Island.[3] The elevated serum IL-6, IL-17, IL-21, and IL-23 levels have been reported in patient with chronic arthritis after chikungunya fever [1,2]. Recent findings in psoriatic arthritis revealed the elevated serum IL-36 during arthritis [4]. IL-36 is a relatively newly found cytokine belonging to the IL-1 family, whose involvement in various diseases is still poorly understood. In the current study, to evaluate the involvement of IL-36 in patients with chikungunya fever, stocked serum from the previously reported two cases [1] at the initial visit, 7 days, and 56 days later were used to measure IL-36α and IL-36βconcentration. Two cases were siblings, and the brother developed pain in his neck and ankle joints on the second day back to Japan, but fever was not detected. Sister developed fever soon after returning to Japan, with severe arthralgia and leg edema. The arthralgia persisted for about a year. IL-36α and IL-36β were measured in the patient's serum using human IL-36α/IL-1F6 and IL-36β/IL-1F8 DuoSet ELISA® (R&D Systems, Minneapolis, MN, USA). At the initial visit, IL-36α was higher in the sister, who had more fever and arthralgia symptoms than her brother. 7 days later, both had higher levels than at the initial visit, but the brother, whose symptoms of Chikungunya fever appeared later, had a larger increase than at the initial visit. After 56 days, both decreased to about half of the peak value. IL-36β was highest at the first visit for both patients and gradually decreased (Figure 1).

3. Discussion

Chikungunya fever causes arthritis, which often persists for a long time in many cases. The sibling patients also suffered from arthralgia even with taking non-steroidal anti-inflammatory drugs. The sister in particular had severe symptoms of arthralgia that persisted for about a year. Based on the results of serum IL-36α and IL-36β levels, the association between IL-36 and chikungunya fever was discussed. Both IL-36α and IL-36β were reduced by 56 days. In the case of psoriatic arthritis, IL-36 activates dendritic cells inducing Th17 cells to generate IL-17 and IL-22, resulting in persistent arthritis. Therefore, the mechanism of chronic arthritis caused by psoriatic arthritis is different from that of chronic arthritis in chikungunya fever and IL-36 may not be involved in the chronic arthritis of chikungunya fever. IL-36α is produced by monocytes, B cells, and T cells. IL-36β is produced by dendritic cells and induces proinflammatory cytokines, including

IL-12, IL-1β, IL-6, and TNF-α. Both IL-36α and IL-36β play an important role in host immunity, and it has been suggested that one physiological function of IL-36 may be to counteract microbial immune evasion [5]. IL-36β was highest at the initial visit, indicating that inflammatory cytokines may have been induced during the infection control process. And IL-36α was persistently high or increased from the time of initial visit to one week, suggesting that the acquired immune mechanism may be the peak. IL-36 might act as an immunological defense mechanism during chikungunya virus infection.

Conflicts of Interests

The authors have declared that no competing interests exist.

Ethics Statement

We had received permission and written informed consent from siblings to use the extra serum for additional testing and publish the current case report.

Funding Statement

The authors did not receive any financial support for this study.

Authors' contributions

Take care of the patient: M.K. Conceptualization and data measurement: M.K. methodology: Y.M. S.I. and T.N. Writing—original draft preparation: M.K. Writing—review and editing: K.H. and K.Y. All authors have read and agreed to the published version of the manuscript.

Data availability Statement

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

References

[1] Kondo M, Akachi S, Ando K, er al., "Two Japanese siblings affected with Chikungunya fever with different clinical courses: Imported infections from the Cook Islands", *J Dermatol* , vol.43, no. 6, pp697-700, 2016.

[2] Chow A, Her Z, Ong EK, et al., "Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor", *J Infect Dis* , vol.203, no.2, pp149-157, 2011.

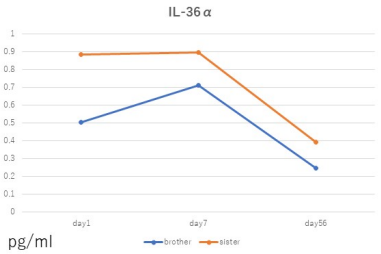
[3] Liu X, Poo YS, Alves JC, et al., "Interleukin-17 Contributes to Chikungunya Virus-Induced Disease", *mBio* , vol.13, no.2, e0028922, 2022.

[4] Boutet MA, Nerviani A, Lliso-Ribera G, et al., "Interleukin-36 family dysregulation drives joint inflammation and therapy response in psoriatic arthritis", *Rheumatology (Oxford)* , vol.59, no.4, pp828-838, 2020.

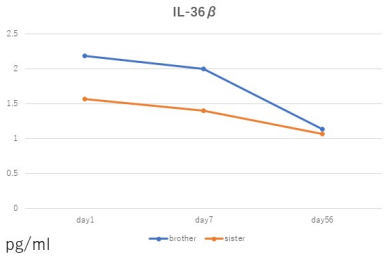
[5] L. E. Jensen, "Interleukin-36 cytokines may overcome microbial immune evasion strategies that inhibit interleukin-1 family signaling",*Sci Signal,* vol.10, no.492, eaan3589, 2017.

Figure legend

FIGURE 1 : The graphs show the changes in serum levels of IL-36α and IL-36β measured on day1 (at first visit), day7, and day56 from the brother and sister. A 20-fold dilution serum was used for the assay.



	brother	sister
day1	0.5066	0.8847
day7	0.7117	0.8959
day56	0.2466	0.3914



	brother	sister
day1	2.185	1.567
day7	2.006	1.408
day56	1.136	1.076