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Original Research Article

Immunological Disturbance in Patients Taking Biology Therapy

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Abstract

Background: Multiple sclerosis is a compound sickness origin via a fundamental interaction compound which is un inheritable factor–environment in addition defined through inflaming toward neurodegenerative the cells of the central nervous system stop working or die demonstration. Alteration the pathologic process and the line of multiple sclerosis due to different molecular modification, which including rises in interleukins, chemokines, NO, species of activated oxygen, self dertermining radicals and glutamate. ***Material & Methods:*** This study included 37 patients taking (5 males ,32 females) and 25 healthy controls. Blood samples were obtained from the biological treatment Unit for neurological diseases in Baghdad Teaching Hospital in the period from November 2023 to March 2024. The serum was isolated by centrifuging blood samples at 1000g for 5 minutes. Human TNF-α levels were quantified using an ELISA kit (Elabscience Biotechnology Inc., USA;133Hu, Lot. no. L240214179.Following the manufacturers protocol. ***Results:*** The results of the present study showed that patients with M.S. had higher levels of TNF-α 34.33 pg/ml while control group had lower levels of TNF-α 28pg/ml, there were a significant difference between patients, P=0.028. ***Conclusion****:* Patients with M.S. had higher levels of TNF-α than their levels in control group, provided a fundamental indication that an increment of TNF-α happen topically inside the central nervous system of patients with M.S.

Keywords: M.S., TNF-α, biology therapy, immunological disturbance.

INTRODUCTION

Millions of people worldwide affecting with M.S. is a chronic immune-mediated and neurodegenerative health problem of the CNS [1] which is the most common cause of non-traumatic neurological impairment in adolescent adults [2]. Complex gene–environment interactions and characterized by multiple pathological hallmarks, ranging from immune dysregulation and neuroinflammation to neurodegenerative mechanisms leading to MS which is a compound multifactorial disease [3]. The pathogenesis and development of MS touch the molecular alteration, which include rises in cytokines, chemokines, nitric oxide, stimulated oxygen species, glutamate, and free radicals [4]. M.S. it is one of the common origin of damage in young adults, since youngest females are exaggerated more than normally, and there are tetrad known courses of illness: relapsing-remitting MS (RRMS), essential advanced MS, secondhand advanced MS, and progressive-relapsing MS. [5].

Theory supported the that soluble aspects (chemokines and cytokines) formed by meningeal tertiary lymphoid constructions and/or present immune cells might diffuse through the cerebrospinal fluid (CSF) into the cortex, inducing brain impairment either directly or indirectly through microglial activation in which researches of molecular- neuropathological on forward MS patients [6] Kosa and colleagues found that CSF biomarkers related to with immune-related paths associate with clinical and imagination multiple sclerosis intensity consequences and guess coming debility [7] .

Neuroaxonal homeostasis distributed contiguously in chronic inflammation in the CNS advocate all these discoveries, leading to prominent neurodegeneration, even external of multiple sclerosis interruption, particularly at the advanced phase. A foremost mechanism driving advanced multiple sclerosis Established that classified inflammation (involving the CSF, meninges, and parenchyma) [8]. Tumor necrosis factor (TNF) represents one of the core proinflammatory

cytokines linked with the grade of debility in patients with progressive multiple sclerosis among the different cytokines found to upsurge in the CSF of multiple sclerosis patients [9].

THE RESULTS

Statistical analyses were performed using SPSS statistical package for Social Sciences (version 20.0 for windows, SPSS, Chicago, IL, USA). Distribution was tested using Shapiro-Wilk test; TNF-a was found to be non-normal. Data are represented as count and percentage for demographic parameters, median IQR (Inter-quartile range) for TNF-a. Mann-Whitney U test was used to study the difference between patient and control groups for TNF-a. P value of <0.5 was considered as significant.

The results of the present study showed in Table (1) that there was 1 patient his age was (2.7%) less than 20 year, while there were 26(70.3%) of patients within age between 20-40 years. Also, there were 10(27.0%) of patients their age were more there age than 40 years. The mean±SD of age was (34.4±11.57) years. According to gender there were 5(13.5%) male, and there were 32(86.5%) females.

Table 1: The ages and sex of patients group

		Count	%
Age	<20y	1	2.7%
	20-40y	26	70.3%
	>40y	10	27.0%
Gender	Male	5	13.5%
	Female	32	86.5%

Age mean (standard deviation) in patients was 34.48 (11.57) years. The results showed in Table (2) that there were26 (70%) of patients group with multiple sclerosis had depression, while there were only 11(29.7%) of patients did not have depression. While there were17(45%) of patients had back pain and 20(54.1%) did not have back pain. In addition there were 17(45.9%) of patients had anemia, and 20 (54.1%) did not have anemia.

Table 2: The demographic features of patients group

		Count	%
UTI	Yes	5	13.5%
	No	32	86.5%
RSI	Yes	22	59.5%
	No	15	40.5%
Depression	Yes	26	70.3%
	No	11	29.7%
Diarrhea	Yes	4	10.8%
	No	33	89.2%
Stomach pain	Yes	11	29.7%
	No	26	70.3%
Skin rash	Yes	7	18.9%
	No	30	81.1%
Abdominal pain	Yes	7	18.9%
	No	30	81.1%
Back pain	Yes	17	45.9%
	No	20	54.1%
Anemia	Yes	17	45.9%
	No	20	54.1%
Pharyngeal pain	Yes	4	10.8%
	No	33	89.2%
Vomiting	Yes	17	45.9%
	No	20	54.1%
Cough	Yes	5	13.5%
	No	32	86.5%
TB	Yes	0	0.0%
	No	37	100.0%
Cancer	Yes	0	0.0%
	No	37	100.0%
Psoriasis	Yes	0	0.0%
	No	37	100.0%
Fistula	Yes	0	0.0%
	No	37	100.0%

The results showed in Table (3) that the mean±SD of TNF-alpha in patients group was 19.01±7.09, with maximum value34.33 pg/ml, while the mean±SD of TNF-alpha was 15.53±4.98 in control group, with maximum value28 pg/ml. There were a significant differences between patients and control patients (P=0.028).

Table 3: The levels of TNF-alpha in patients and control groups

	Group							
	Patient				Control			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
TNF-a pg/Ml	19.01	7.09	4.16	34.33	15.53	4.98	9.50	28.00

The results showed in Figure (1) that the levels of TNF-alpha in patients group were higher than the levels of TNF-alpha in control group.

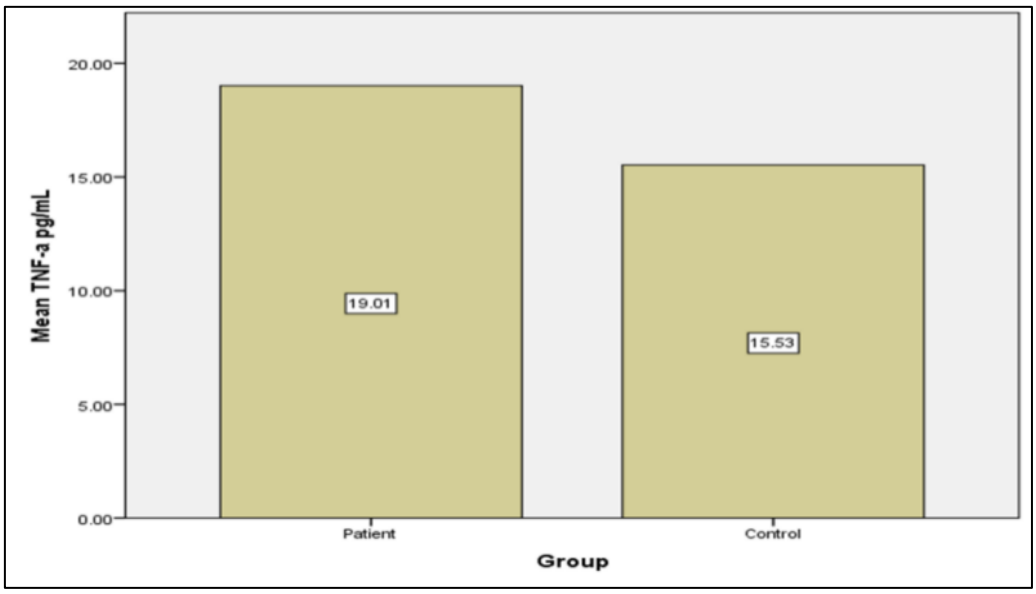

Figure 1

DISCUSSION

The results of the present study revealed that the levels of TNF-α were high in patients with MS than in control group, since the mean ±SD of TNF-α levels was 19±7.0,while the mean ±SD of TNF-α levels in control group was 15.3±4.98,these results in agreement with that reported by Selmaj *et al*. who reported that there was an important suggestion that an arise in TNF levels happened locally inside the CNS of patients with M.S, exactly in acute and chronic active phase of MS brain lesions . This more submit is demyelination and neurodegeneration that the together of inflammation is a highly specific process in multiple sclerosis, and these results in agreement with that reported by Fischer *et al.,* [10] that strong proinflammatory TNF shows its activity by activating two specific TNF receptors (TNFRs): TNF receptor type-1 (TNFR1) and type-2 (TNFR2) signaling [11,12]. Excitotoxic and necro-apoptotic effects that caused by TNF on oligodendrocytes and neurons mainly through TNFR1 activation. In addition to this inflammatory action [13-16].

The strong link between localized inflammation and the increased expression of genes involved in the TNFR1 signaling pathway. Since there were an disequilibrium between TNF receptor type-1 (TNFR1) and type-2 (TNFR2) signaling contributes to the severity of MS.

A post-mortem study discovered that [17]. Also, the results of the present study showed that there were 26(70.3%) of patients afflicted with MS had depression, while there were 11(29.7%) of patients with M.S. did not have depression. These results in agreement with that reported by (Scott B. *et al.*, 2017) that up and around to 50% of people living with depressing disorders had multiple sclerosis (MS). Occurrence guesses are generally 2–3-times higher than those of the general people. Numerous aetiologic features may donate to the etiology of depression in MS, including biological mechanisms (*e.g.* hippocampal microglial activation, lesion burden, regional atrophy), as well as the stressors, threats, and losses that go together with a live with an impulsive and frequently deactivating illness. Approximately protruding risk feature for hopelessness such as (younger) age, (female) sex, and family history of depression are less inconsistently connected with depression in MS than they are in the general pe ople [18].

In addition, the results of the current study showed that there were 32(86.5%) females, while there were 5(13.5%) male, these results in agreement with that reported by Pleines P. *et al,* 2015, who reported that many diseases with an auto-immune etiology have a skewed sex distribution. In the majority of instances, women are affected more frequently than men. A review of population studies demonstrates that the

preponderance of women in multiple sclerosis (MS) is almost constant [19-22].

REFERENCES

1. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV,Thompson AJ. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology.* 2014;83(11):1022–4. https//:doi. org/ 10. 1212/ WNL. 00000 00000 000768.
2. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol*. 2010;9(5):520–32.https:// doi. org/ 10. 1016/ S1474- 4422(10) 70064-8.
3. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA.Multiple sclerosis. *Nat Rev Dis Primers.* 2018;4(1):43. https:// doi. org/101 . /1038 /s41572- 018- 0041-4.
4. Wan ECK. Cellular and molecular mechanisms in the pathogenesis of multiple sclerosis. Cells. 2020;9(10):2223. https:// doi. org/ 10. 3390/ cells.2391022
5. Overview (multiple sclerosis). November, 2020: https://www.nhs.uk/conditions/multiplesclerosis/2018.
6. Magliozzi R, Howell OW, Nicholas R, Cruciani C, Castellaro M, Romualdi C, Rossi S, Pitteri M, Benedetti MD, Gajofatto A, *et al*. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. *Ann Neurol.* 2018;83(4):739–55. https:// doi. org/ 10. 1002/ ana. 25197.
7. Kosa P, Barbour C, Varosanec M, Wichman A, Sandford M, Greenwood M,Bielekova B. Molecular models of multiple sclerosis severity identify heterogeneity of pathogenic mechanisms. *Nat Commun.*2022;13(1):7670,https:// doi. org/ 10. 1038/ s41467- 022- 35357-4.
8. Calabrese M, Magliozzi R, Ciccarelli O, Geurts JJ, Reynolds R, Martin R.Exploring the origins of grey matter damage in multiple sclerosis. *Nat Rev Neurosci.* 2015;16(3):147–58. https:// doi. org/ 10. 1038/ nrn39 00.
9. Selmaj K, Raine CS, Cannella B, Brosnan CF. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. *J Clin Invest.* 1991;87(3):949–54. https:// doi. org/ 10. 1172/ JCI11 5102.
10. Fischer MT, Wimmer I, Höftberger R, Gerlach S, Haider L, Zrzavy T,Hametner S, Mahad D, Binder CJ, Krumbholz M, Bauer J, Bradl M, Lassmann H. Disease-specific molecular events in cortical multiple sclerosis lesions. *Brain*.2013;136(Pt 6):1799–815. https:// doi. org/ 10. 1093/ brain/awt110.
11. Zahid M, Busmail A, Penumetcha SS, Ahluwalia S, Irfan R, Khan SA ,Rohit Reddy S, Vasquez Lopez ME, Mohammed L. Tumor necrosis factor alpha blockade and multiple sclerosis: exploring new avenues. Cureus 2021;13(10): e18847. https:// doi. org/ .
12. Navikas V, Link H. Cytokines and the pathogenesis of multiple sclerosis[review]. *J Neurosci Res.* 1996;45:322–33.
13. Olmos G, Lladó J. Tumor necrosis factor alpha: a link between neuroinflammation and excitotoxicity. *Mediators Inflamm*. 2014;2014: 861231.https:// doi. org/ 10.
14. Akassoglou K, Bauer J, Kassiotis G, Pasparakis M, Lassmann H, Kollias,G, Probert L. Oligodendrocyte apoptosis and primary demyelination induced by local TNF/p55TNF receptor signaling in the central nervous system of transgenic mice: models for multiple sclerosis with primary oligodendrogliopathy. *Am J Pathol.* 1998;153(3):801–13. https:// doi. org/10. 1016/ S0002- 9440(10) 65622-2.
15. Ofengeim D, Ito Y, Najafov A, Zhang Y, Shan B, DeWitt JP, Ye J, Zhang X,Chang A, Vakifahmetoglu-Norberg H, *et al.* Activation of necroptosis in multiple sclerosis. *Cell Rep.* 2015;10(11):1836–49. https:// doi. org/ 10.1016/j .
16. Picon C, Jayaraman A, James R, Beck C, Gallego P, Witte ME, van Horssen J, Mazarakis ND, Reynolds R. Neuron-specific activation of necroptosis signaling in multiple sclerosis cortical grey matter. *Acta Neuropathol*.2021;141(4):585–604. https:// doi. org/ 10. 1007/ s00401- 021- 02274-7.
17. Magliozzi R, Howell OW, Durrenberger P, Arico E, James R, Cruciani C,Reeves C, Roncaroli F, Nicholas R, Reynolds R. Meningeal inflammation changes the balance of TNF signalling in cortical grey matter in multiple sclerosis. *J Neuroinflammation.* 2019;16(1):259. https:// doi. org/10. 1186/ s12974- 019- 1650-x.
18. Scott B. Patten,Ruth Ann Marrie &Mauro G. Carta. The Burden of Co-Morbidity of Psychiatric Disorders in Chronic Medical Illness. International Review of Pschiatry,2017; volume 29, issue 5: Pages 463-472.
19. Pleines P. Duquette, M. Girard, L. Charest M. Senecal-Quevillon, The increased susceptibility of women to multiple sclerosis, Can J Neurol Sci. 1992Nov;19(4):466-71.DOI: https://doi.org/10.1017/S0317167100041664
20. Valentina Mazziotti, Francesco Crescenzo, Ermanna Turano, Maddalena Guandalini, Maddalena Bertolazzo, Stefano Ziccardi, Federica Virla, Valentina Camera, Damiano Marastoni, Agnese Tamanti & Massimiliano Calabrese,2024: The contribution of tumor necrosis factor to multiple sclerosis: a possible role in progression independent of relapse? *Journal of Neuroinflammation* ,volume 21, Article number: 209 ,https://doi.org/10.1186/s12974-024-03193-6
21. Maryam Zahid ,Alberto Busmail, Sai Sri Penumetcha, Saher Ahluwalia, Rejja Irfan, Sawleha Arshi Khan, Sai Rohit Reddy, Maria Elisa Vasquez

Lopez, Lubna Mohammed,2021: Tumor Necrosis Factor Alpha Blockade and Multiple Sclerosis: Exploring New Avenues, *Cureus.* 17;13(10):e18847. doi: 10.7759/cureus.18847).

22. Sharief MK, Hentges R. Association between tumor necrosis factoralpha and disease progression in patients with multiple sclerosis. *N.Engl J Med*. 1991;325(7):467–72. https:// doi. org/ 10. 1056/ NEJM1 99108 15325 0704.