International Immunopharmacology 75 (2019) 105793

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Proportions of Th17 cells and Th17-related cytokines in neuromyelitis optica spectrum disorders patients: A meta-analysis

Miao-Miao Hou[a,1], Yu-Feng Li[b,c,1], Ling-Ling He[a], Xiao-Qiong Li[a], Yu Zhang[d,e], Sheng-Xiao Zhang[f], Xin-Yi Li[a,*]

[a] Department of Neurology, Shanxi Dayi Hospital Affiliated to Shanxi Medical University, 99 Longcheng Street, Taiyuan, Shanxi 030024, China
[b] Department of Neurology and Stroke Center, The First Affiliated Hospital of Jinan University, Jinan University, Guangzhou 510630, China
[c] Clinical Neuroscience Institute of Jinan University, Jinan University, Guangzhou 510630, China
[d] Key Laboratory of Cellular Physiology, Shanxi Medical University, Ministry of Education, Taiyuan 030001, China
[e] Department of Physiology, Shanxi Medical University, Taiyuan 030001, China
[f] Department of Rheumatology, the Second Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China

ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorders
Th17
Th17-associated cytokines
Meta-analysis

ABSTRACT

Background: T helper (Th17) cells play an important role in many autoimmune diseases. In this meta-analysis, we aimed to specify the proportion of Th17 cells and the levels of Th17-related cytokines in neuromyelitis optica spectrum disorders (NMOSD) patients, we did this meta-analysis.

Methods: Using previously reported data from PubMed, EMBASE, and Web of Science and Cochrane, we explored the proportion of Th17 cells in $CD4^+$ T cells in peripheral blood (PB) and the level of Th17-related cytokines, such as interleukin (IL)1β, IL6, IL17, IL21, IL22, IL23 and transforming growth factor -beta (TGFβ), in cerebrospinal fluid (CSF), plasma, and serum in NMOSD patients compared to control group and multiple sclerosis (MS) patients.

Results: In total, 38 trials were included for our analysis. Results showed that the proportion of Th17 cells was higher in NMOSD patients than in the control and MS groups. The levels of IL1β, IL6, IL17 and IL21 in CSF and plasma, and IL6, IL21, IL22, and IL23 in the serum were higher in NMOSD patients than in the control group. The levels of IL6 in CSF and serum and IL17 in plasma and serum were higher in NMOSD patients than in MS patients.

Conclusion: The proportion of Th17 cells and the levels of Th17-related cytokines was increased in NMOSD patients compared with the control group and MS patients. The results of this meta-analysis indicated that Th17 cells and Th17-associated cytokines may play an essential role in the pathogenesis of NMOSD.

PROSPERO registration: CRD42019128785.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a heterogeneous autoimmune disease of the central nervous system (CNS), including the spinal cord, optic nerve, and brain stem, and leads to severe disability such as blindness or paraplegia [1]. Understanding the pathogenesis of NMOSD, and identifying the possible targets for its intervention, is, therefore, a requisite.

The discovery of the pathogenic serum antiaquaporin-4 (AQP4) antibody has led to leading to great advances in NMOSD, and the International Panel for NMD diagnosis (IPND) proposed a stratified diagnosis of NMSOD based on anti-AQP4 [1]. However, studies have shown that transferring anti-AQP4 antibodies alone could not induce NMO pathological changes in experimental animals, and required a simultaneous induction of T cell inflammation, suggesting the plausible role of T cells in the underlying pathogenesis of NMOSD [2].

Recent studies have shown that Th17 and Th17-related cytokines, such as interleukin 1-beta (IL1β), interleukin 6 (IL6), interleukin 6 (IL6), interleukin 17 (IL17), interleukin 21 (IL21), interleukin 22 (IL22), interleukin 23 (IL23), and transforming growth factor -beta (TGFβ), are linked to the progression of multiple sclerosis (MS) and NMOSD [3–6]. Th17 cells are T cells with a highly pro-inflammatory effect and produce high levels of IL17, IL21, IL22, IL23, and others [7].

Th17 cells are induced by a combination of IL6 and TGFβ; IL6 is a

* Corresponding author.
E-mail address: xinyili2003@163.com (X.-Y. Li).
[1] These authors contributed to the work equally and should be regarded as co-first authors.

https://doi.org/10.1016/j.intimp.2019.105793
Received 29 May 2019; Received in revised form 24 July 2019; Accepted 29 July 2019
Available online 08 August 2019

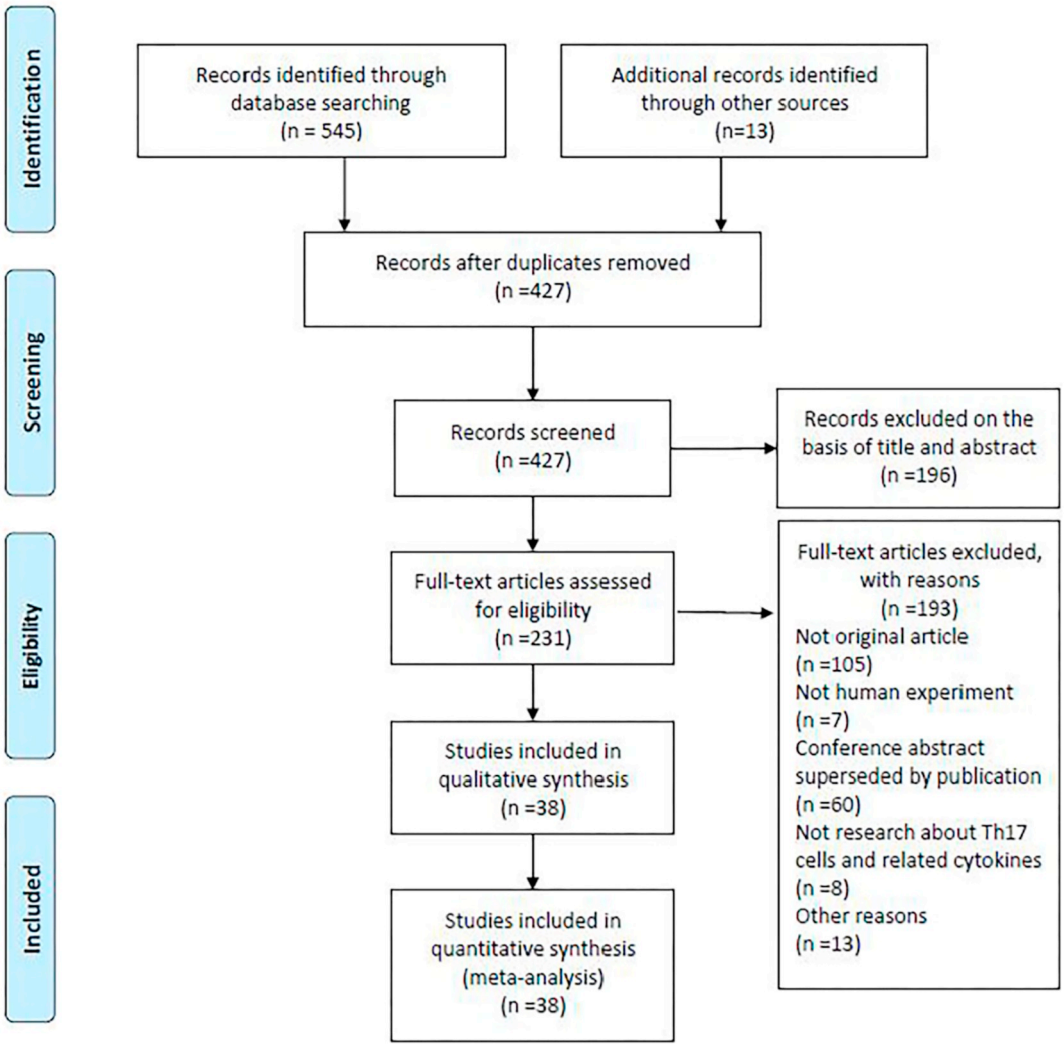


Fig. 1. Study selection process.

pro-inflammatory cytokine, and promotes the differentiation of naive T cells into cytotoxic T cells or Th17 cells, and activate the synthesis of immunoglobulin (Ig) in B cells [8]. IL21 can enhance Th17 cells' precursor frequency [9–11].IL17 is a pro-inflammatory effector cytokine that induces the expression of chemokines and attracts neutrophilic leukocytes [12,13]. The induction of inflammation auto reactiveness of Th17 cells are activated by IL23 [14,15]. IL1β can activate cAMP-response element binding protein (CREB) and NFκB promoter, and might be one of the factors inducing severe lesions in NMOSD.

Even though our previous study results suggested the MS patients have a higher proportion of Th17 cells and higher levels of IL-17 and IL-23 [16], the proportion of Th17 cells and level of Th17-related cytokines in NMOSD patients remains unknown [3–5,17–24]. Based on the above reasons, we reviewed the related original studies systemically and conducted this meta-analysis.

2. Methods

2.1. Search strategy and selection criteria

This meta-analysis was carried out based on the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25] and was registered on the international prospective register of systematic reviews (PROSPERO) (CRD42019128785).

Two researchers searched PubMed, EMBASE, Web of Science, and Cochrane independently. The Medical Subject Headings (MeSH), “Neuromyelitis Optica”, “Th17 Cells”, “Interleukin-1beta”, “Interleukin-6”, “Interleukin-17”, “Interleukin-21”, “Interleukin-22”, “Interleukin-23”, “Transforming Growth Factor beta” and related free words were used to search relevant papers. We also checked the related reference in related reviews and included studies, to find any papers that might be overlooked. All studies published before May 18, 2019, were used for the analysis.

2.2. Study selection

Inclusion criteria: 1) original studies; 2) full text published in English; 3) studies on human subjects; 4) The MeSH terms and related free words about“Neuromyelitis Optica” and “‘Th17 Cells’ or ‘Interleukin-1beta’ or ‘Interleukin-6’or ‘Interleukin-17’ or ‘Interleukin-21’ or ‘Interleukin-22’ or ‘Interleukin-23’ or ‘Transforming Growth Factor beta’ are included in title or abstract; 5) studies reporting the proportion of Th17 cells or levels of Th17-related cytokines in NMOSD; 6) studies that have a control group or using MS patients as control.

Exclusion criteria: 1) non-original studies; 2) multiple publications or overlapping subjects; 3) incomplete or non-retrievable data; 4) studies with no suitable comparison group; 5) conference abstract superseded publication; 6) does not include study on the proportion of Th17 cells and level of Th17-related cytokines in NMOSD patients; 7) case report.

Table 1
Characteristics of included study.

Study	Country	Case number	Age (years)	Age at onset (years)	Duration of disease (years)	Sex (F/M)	No. of relapses	EDSS	Q	Control group
(Takaaki Ishizu, 2005) [28]	Japan	NMOSD: 20	NMOSD: 41.5 ± 15.9	NMOSD: 44.2 ± 16.9	NMOSD: 6.3 ± 5.4	NMOSD:19/1	NMOSD: 7.3 ± 5.1	NMOSD: 5.5 ± 2.3	8	ONNDs
		MS: 20	MS: 41.5 ± 15.9	MS: 25.8 ± 8.9	MS: 6.1 ± 7.1	MS: 16/4	MS: 6.1 ± 5.7	MS: 4.0 ± 1.8		
		CTL: 19	CTL: 59.4 ± 10.9	-	-	CTL: 10/9	-	-		
(Akiyuki Uzawa, 2009) [29]	Japan	NMOSD: 17	NMOSD: 49.6	-	-	NMOSD:17/0	-	-	6	ONDs
		MS: 21	MS: 30.9	-	-	MS: 17/4	-	-		
		CTL: 21	CTL: 57.1	-	-	CTL: 12/9	-	-		
(K. Yanagawa, 2009) [30]	Japan	NMO(MY): 8	-	NMO(MY): 44.5	NMO(MY): 4.8 ± 4.5	NMO(MY): 8/0	NMO(MY): 2.1 ± 1.3	NMO(MY): 5.2 ± 2.8	8	-
		NMOSD: 9	-	NMOSD: 24.0	NMOSD: 16.7 ± 10.5	NMOSD: 8/1	NMOSD: 9.1 ± 5.5	NMOSD: 5.3 ± 2.2		
		MS: 13	-	-	-	-	-	-		
(Sema Icoz, 2010) [31]	Turkey	NMOSD: 23	NMOSD: 36.35 ± 5.06	NMOSD: 29.74 ± 6.8	NMOSD: 11.04 ± 2.86	NMOSD:17/6	-	-	6	Neurologically normal controls
		MS: 27	-	-	-	-	-	-		
		CTL: 20	-	-	-	-	-	-		
(Akiyuki Uzawa, 2010)[32]	Japan	NMOSD: 31	NMOSD: 48.7	-	NMOSD: 9.3	NMOSD:31/0	-	NMOSD: 7.5	8	ONDs
		MS: 29	MS: 30.6	-	MS: 3.75	MS: 22/7	-	MS: 3.5		
		CTL: 18	CTL: 57.7	-	-	CTL: 11/7	-	-		
(Ying Li, 2011) [33]	China	NMOSD: 16	NMOSD: 34.60 ± 14.87	-	NMOSD: 1	NMOSD:10/6	NMOSD: 2.93 ± 1.22	NMOSD: 4.36 ± 2.0	7	ONNDs
		MS: 14	MS: 34.60 ± 14.11	-	MS: 0.88	MS: 9/5	MS: 3.33 ± 2.13	MS: 2.83 ± 0.86		
		CTL: 16	CTL: 35.31 ± 13.65	-	-	CTL: 12/4	-	-		
(H.H. Wang, 2011) [34]	China	NMOSD: 14	NMOSD: 35.78	-	NMOSD: 6.31	NMOSD:10/4	-	NMOSD: 3.82	7	HC
		MS: 20	MS: 32.05	-	MS: 5.95	MS: 14/6	-	MS: 3.75		
		CTL: 16	CTL: 34.31	-	-	CTL: 11/5	-	-		
(Canan Ulusoy, 2012) [35]	Turkey	NMOSD: 18	NMOSD: 39.85 ± 5.91	-	-	NMOSD:15/3	-	-	6	HC
		CTL: 30	CTL: 40.21 ± 5.18	-	-	CTL: 21/9	-	-		
(K.-C. WANG, 2012) [36]	China	NMOSD: 29	NMOSD: 41.5 ± 9.7	-	NMOSD: 5	NMOSD:28/1	NMOSD: 5	NMOSD: 3.0	6	-
		MS: 20	MS: 41.7 ± 12.6	-	MS: 4	MS: 16/4	MS: 2	MS: 2.8		
(Aimin Wu, 2012) [37]	China	NMOSD: 21	NMOSD: 34.0	NMOSD: 32.0	NMOSD: 3.0	NMOSD:16/5	-	NMOSD: 4.0	8	ONNDs
		MS: 20	MS: 35.5	MS: 32.0	MS: 3.5	MS: 13/7	NMOSD: 1.0/year	MS: 2.3		
		CTL: 16	CTL: 34.5	-	-	CTL: 9/7	MS: 0.59/year	-		
(Takuya Matsushita, 2013) [38]	Japan	NMOSD: 20	NMOSD: 49.1 ± 11.4	-	NMOSD: 10.6 ± 9.7	NMOSD:17/3	-	NMOSD: 5.6 ± 2.5	8	ONDs
		MS: 35	MS: 39.77 ± 12	-	MS: 9.17 ± 10.6	MS: 20/15	-	MS: 4.45 ± 1.98		
		CTL: 18	CTL: 46.3 ± 17.5	-	-	CTL: 6/12	-	-		
(B.D. Michael, 2013) [39]	UK	NMOSD: 19	NMOSD: 50	-	NMOSD: 9.53	NMOSD:2/17	-	NMOSD: 4	7	-
		MS: 10	MS: 38	-	MS: 5.17	MS: 3/7	-	MS: 4.25		
(Akiyuki Uzawa, 2013) [40]	Japan	NMOSD: 42	NMOSD: 51.5	-	NMOSD: 10.79	NMOSD:39/3	-	NMOSD: 5.8	8	ONNDs
		MS: 30	MS: 33.2	-	MS: 5.93	MS: 21/9	-	MS: 3.5		
		CTL: 30	CTL: 59.1	-	-	CTL: 11/19	-	-		
(Honghao Wang, 2013) [27]	China	NMOSD: 26	NMOSD: 38.04 ± 12.70	NMOSD: 33.00 ± 13.53	-	NMOSD:17/9	NMOSD: 0.81/year	NMOSD: 3.88 ± 1.95	8	HC
		MS: 23	MS: 37.35 ± 11.43	MS: 31.13 ± 11.47	-	MS: 14/9	MS: 0.64/year	MS: 3.04 ± 1.86		
		CTL: 22	CTL: 36.68 ± 8.80	-	-	CTL: 14/8	-	-		
(Honghao Wang, 2013) [41]	China	NMOSD: 22	NMOSD: 35.5	NMOSD: 32	NMOSD: 3	NMOSD:16/6	NMOSD: 1.0/year	NMOSD: 3.5	8	ONNDs
		MS: 18	MS: 35.5	MS: 30	MS: 4	MS: 11/7	MS: 0.5/year	MS: 2.75		
		CTL: 14	CTL: 50	-	-	CTL: 8/6	-	CTL: 1		
(Kai Chen Wang, 2013) [42]	China	NMOSD: 34	NMOSD: 47.0	-	-	NMOSD: 32/2	NMOSD: 1.0/year	NMOSD: 4.5	6	HC
		MS: 24	MS: 42.0	-	-	MS: 20/4	MS: 0.6/year	MS: 2.5		
		CTL: 30	-	-	-	-	-	-		
(Wen Xu, 2013) [43]	China	NMOSD: 21	NMOSD: 36.14 ± 13.42	-	NMOSD: 3.93	NMOSD: 17/4	NMOSD: 1.2/year	NMOSD: 3.47 ± 1.06	7	HC
		MS: 15	MS: 35.33 ± 7.87	-	MS: 3.87	MS: 10/5	MS: 0.9/year	MS: 3.43 ± 1.33		
		CTL: 12	CTL: 35.25 ± 14.57	-	-	CTL: 9/3	-	-		

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Case number	Age (years)	Age at onset (years)	Duration of disease (years)	Sex (F/M)	No. of relapses	EDSS	Q	Control group
(Philippe Horellou, 2015) [44]	France	NMOSD: 17	-	NMOSD: 9 ± 5	-	NMOSD: 11/6	-	NMOSD: 0.6 ± 1.7	7	ONDs
		MS: 17	-	MS: 12 ± 2	-	MS: 15/2	-	MS: 1.0 ± 1.4		
		CTL: 12	-	CTL: 7 ± 5	-	CTL: 7/5	-	-		
(Kunihiro Ichinose, 2015) [45]	Japan	NMOSD: 22	-	-	-	-	-	-	5	-
		MS: 20	-	-	-	-	-	-		
(Yu-Jing Li, 2015) [46]	China	NMOSD: 35	NMOSD: 46.54 ± 13.07	-	NMOSD: 7.00 ± 7.40	NMOSD: 30/5	NMOSD: 4.77 ± 3.87	NMOSD: 4.53 ± 2.51	8	HC
		MS: 20	MS: 39.85 ± 12.14	-	MS: 4.95 ± 6.23	MS: 13/7	MS: 3.00 ± 2.41	MS: 2.50 ± 1.42		
		CTL: 20	CTL: 48.40 ± 14.28	-	-	CTL: 18/2	-	-		
(Fumitaka Shimizu1, 2015) [47]	Japan	NMOSD: 28	NMOSD: 53.2	-	NMOSD: 3.9	-	NMOSD: 3.0	-	6	HC
		MS: 6	MS: 37.8	-	MS: 4.5	MS: 3/3	MS: 3.0	-		
		CTL: 10	CTL: 32.6	-	-	CTL: 6/4	-	-		
(P. O. Barros, 2016) [48]	France	NMOSD: 20	NMOSD: 42.2 ± 12.3	-	NMOSD: 7.2 ± 4.59	NMOSD:16/4	NMOSD: 11	NMOSD: 4.93 ± 1.91	7	HC
		CTL: 20	CTL: 39.6 ± 10.3	-	-	CTL: 16/4	-	-		
(Xueli Fan, 2016) [49]	China	NMOSD: 25	NMOSD: 51	-	NMOSD: 1	NMOSD: 22/3	NMOSD: 2	NMOSD: 3.5	8	HC
		CTL: 17	CTL: 47	-	-	CTL: 15/2	-	-		
		NMOSD: 15	NMOSD: 53	-	-	NMOSD: 14/1	-	-		ONNDs
		CTL: 8	CTL: 39	-	-	CTL: 7/1	-	-		
(Kimitoshi Kimura, 2016) [50]	Japan	NMOSD: 7	-	-	-	-	-	-	5	HC
		MS: 27	MS: 42.5	-	MS: 11.0 ± 16.2	MS: 20/7	MS: 0.48/year	-		
		CTL: 8	-	-	-	-	-	-		
(Yuge Wang, 2016) [51]	China	NMOSD: 8	NMOSD: 42	NMOSD: 38.25	NMOSD: 4.1	NMOSD: 6/2	NMOSD: 0.58/year	NMOSD: 2.63	8	ONNDs
		MS: 8	MS: 45	MS: 38	MS: 4.8	MS: 6/2	MS: 0.27/year	MS: 2.86		
		CTL: 8	CTL: 40	-	-	CTL: 6/2	-	-		
(Tao Yang, 2016) [52]	China	NMOSD: 25	NMOSD: 36.80 ± 2.45	NMOSD: 30.24 ± 2.34	NMOSD: 6.04 ± 1.01	NMOSD: 23/2	NMOSD: 1.69/year	NMOSD: 3.24 ± 0.35	7	HC
		MS: 25	MS: 33.84 ± 2.31	MS: 29.84 ± 2.28	MS: 3.92 ± 0.53	MS: 19/6	MS: 1.61/year	MS: 1.92 ± 0.28		
		CTL: 20	CTL: 32.3 ± 1.80	-	-	CTL: 15/5	-	-		
(Qiuming Zeng, 2016) [53]	China	NMOSD: 22	NMOSD: 40.7 ± 15.87	NMOSD: 37.6 ± 16.1	-	NMOSD: 17/5	NMOSD: 1.6	-	7	HC
		CTL: 15	CTL: 42.5 ± 12.77	-	-	CTL: 11/4	-	-		
		NMOSD: 22	NMOSD: 40.7 ± 15.87	NMOSD: 37.6 ± 16.1	-	NMOSD: 17/5	-	-		ONNDs
		CTL: 9	CTL: 42.1 ± 14.18	-	-	CTL: 7/2	-	-		
(Priscila O. Barros, 2017) [22]	Brazil	NMOSD: 20	NMOSD: 43.1 ± 18.1	-	-	NMOSD: 2/18	-	NMOSD: 5.1	8	HC
		CTL: 20	CTL: 41.1 ± 20.1	-	-	CTL: 2/18	-	-		
(Akio Kimura, 2017) [24]	Japan	NMOSD: 15	NMOSD: 47.9 ± 14.6	-	NMOSD: 0.3	NMOSD: 14/1	-	NMOSD: 6	8	ONDs
		MS: 17	MS: 44.2 ± 12.7	-	MS:5	MS: 13/4	-	MS: 5		
		CTL: 20	CTL: 35.2 ± 15.7	-	-	CTL: 8/12	-	-		
(Tomohiko Uchida, 2017) [4]	Japan	NMOSD: 28	NMOSD: 52	-	NMOSD: 5.42	NMOSD: 27/1	-	NMOSD: 6.0	7	ONDs
		MS: 29	MS: 36	-	MS: 4.08	MS: 23/6	-	MS: 2.5		
		CTL: 27	-	-	-	-	-	-		
(Akiyuki Uzawa, 2017) [5]	Japan	NMOSD: 59	NMOSD: 51.6 ± 14.6	-	-	NMOSD: 50/9	-	-	7	INDs
		MS: 76	MS: 38.3 ± 10.8	-	-	MS: 56/20	-	-		
		CTL: 70	CTL: 47.7 ± 18.6	-	-	CTL: 35/35	-	-		
(Cong Zhao, 2017) [23]	China	NMOSD: 31	NMOSD: 44.94 ± 3.7	-	NMOSD: 3.61 ± 0.85	NMOSD: 29/2	-	-	7	HC
		CTL: 18	CTL: 41.61 ± 2.18	-	-	CTL: 16/2	-	-		
(Ryotaro Ikeguchi, 2018) [20]	Japan	NMOSD: 35	NMOSD: 39	-	NMOSD: 2.4	NMOSD:31/4	-	NMOSD: 5.0	8	-
		MS: 64	MS: 30	-	MS: 4.3	MS: 44/20	-	MS: 3.0		
(Shanshan Pei, 2018) [21]	China	NMOSD: 23	NMOSD: 33.43	-	NMOSD: 2.24	NMOSD: 15/8	-	NMOSD: 4.22	8	ONNDs
		MS: 12	MS: 34.58	-	MS: 1.75	MS: 5/7	-	MS: 2.25		
		CTL: 16	CTL: 33.88	-	-	CTL: 11/5	-	-		
(Nanping Ai, 2019) [19]	China	NMOSD: 43	NMOSD: 35.65 ± 4.8	-	-	NMOSD: 30/13	-	-	7	HC
		CTL: 16	CTL: 30.23 ± 2.35	-	-	-	-	-		

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Case number	Age (years)	Age at onset (years)	Duration of disease (years)	Sex (F/M)	No. of relapses	EDSS	Q	Control group
(Baozhu Liu, 2019) [18]	China	NMOSD: 31	NMOSD: 38.0	NMOSD: 31.0	NMOSD: 3.0	NMOSD: 20/11	NMOSD: 1.0/year	NMOSD: 4.5	8	ONNDs
		MS: 23	MS: 38.0	MS: 32.0	MS: 4.0	MS: 10/13	MS: 0.6/year	MS: 2.5		
		CTL: 22	CTL: 35.5	-	-	CTL: 14/8	-	-		
(Clarice Monteiro, 2019) [17]	Brazil	NMOSD: 26	NMOSD: 41.1	-	NMOSD: 6.7	NMOSD: 14/12	-	NMOSD: 4.2	8	HC
		CTL: 25	CTL: 39.4	-	-	CTL: 13/12	-	-		
(Yuzhen Wei, 2019) [3]	China	NMOSD: 18	NMOSD: 45.54 ± 14.3	-	-	NMOSD: 15/3	-	NMOSD: 6.23 ± 1.71	8	ONNDs
		MS: 8	MS: 37.4 ± 15.0	-	-	MS: 5/3	-	MS: 3.3 ± 1.4		
		CTL: 15	CTL: 40.2 ± 9.6	-	-	CTL: 13/2	-	-		

NMOSD: neuromyelitis optica spectrum disorders; MS: multiple sclerosis; F: female; M: male; Q: quality; CSF: cerebrospinal fluid; EDSS: expanded disability status scale; CTL: control group; HC: healthy controls; ONDs: other neurological diseases; ONNDs: other non-inflammatory neurological diseases; INDs: inflammatory neurological disorders; NMO (MY): myelitis positivity of anti-AQP4 antibody in serum, but without optic nerve involvement.

2.3. Data extraction and quality assessment

Two independent researchers (Miaomiao Hou, Yufeng Li) reviewed the studies and extracted data. Disagreements would be resolved under discussion with the third investigator (Lingling He). We extracted the following information from all selected studies: author, published year, country, case number, mean age, age at onset, duration of disease, sex (female/male), number of relapses, score of expanded disability status scale (EDSS), ratio of Th17 cells in $CD4^+$ T cells, sample for testing cytokines, the levels of Th17-related cytokines (IL1β, IL6, IL17, IL21, IL22, IL23, and TGFβ) in cerebrospinal fluid (CSF), plasma, and serum, and the type of control group. The Newcastle–Ottawa Quality Assessment Scale (NOS) [26] was used to evaluate the quality (Q) of each study.

2.4. Statistical analysis

The outcomes were all continuous variables: the proportion of Th17 cells in $CD4^+$ T cells and the levels of IL1β, IL6, IL17, IL21, IL22, IL23, and TGFβ in CSF, plasma, and serum. We used standardized mean differences (SMD) and 95%CI to assess the proportion of Th17 cells and the levels of Th17-related cytokines in NMOSD patients compared to the control group and in MS patients.

Begg's and Egger's tests were used in assessing the asymmetry of the funnel plot. A $P < 0.05$ was considered as publication bias, and if present, the trim-and-fill method was adopted to determine the influence of publication bias on results. The Q test and I^2 test were used to value the heterogeneity. A $P \geq 0.1$ or $I^2 \leq 50\%$ was considered as no significant heterogeneity, and the fixed-effects model (FEM) was applied; the random-effects model (REM) was used, otherwise. We used the sensitivity analysis to value the robustness. Stata (version 14.0) was used for the statistical analyses and images.

3. Results

3.1. Study characteristics

After searching databases of PubMed, EMBASE, Web of Science and Cochrane, along with the manual searching, a total of 558 studies were identified, of which 38 studies were included in this meta-analysis according to the inclusion criteria and exclusion criteria. The screening process is shown in Fig. 1, and the details about the 38 studies are described in Tables 1 and 2. The age of NMOSD patients was higher than that of MS patients [0.44, (0.14, 0.74), $P = 0.004$], while no significant difference was observed between NMOSD patients and control subjects [0.29, (−0.02, 0.60), $P = 0.066$]. There was no significant difference in the duration of disease [0.09, (−0.32, 0.50), $P = 0.662$] and number of relapses [0.23, (−0.13, 0.59), $P = 0.209$] between NMOSD patients and MS patients. The score of EDSS of NMOSD patients was higher than that of MS patients [0.98, (0.33, 1.62), $P = 0.003$]. The percent of female was higher in the NMOSD patients than in the MS group [2.29, (1.71, 3.07), $P < 0.001$] and control subjects [2.23, (1.83, 3.09), $P < 0.001$] (figures are not shown).

3.2. The proportion of Th17 cells

Of the 38 studies included in the meta-analysis, eight studies reported the proportion of Th17 cells in CD4+ T cells in the peripheral blood (PB). The results showed that the proportion of Th17 cells was higher in NMOSD patients was higher than in control subjects and MS patients [0.87, (0.03, 1.44), $P = 0.003$] (Fig. 2); a significant differences was observed when comparing individual MS patients [1.27, (0.18, 2.37), $P = 0.023$] and control subjects [0.52, (0.30, 1.44), $P = 0.013$] (Fig. 2) as well. The heterogeneity among the studies was high (I^2 75.2%, $P < 0.05$), therefore, REM was considered. Due to the small number of included studies, we did not perform funnel plot and

Table 2
The proportion of Th17 cells and the levels of Th17-related cytokines in NMOSD, MS and control group.

Study	% of Th17 cells	Sample for cytokines	IL-1β (pg/ml)	IL-6 (pg/ml)	IL-17 (pg/ml)	IL-21 (pg/ml)	IL-22 (pg/ml)	IL-23 (pg/ml)	TGF-β (pg/ml)
(Takaaki Ishizu, 2005) [28]	–	CSF	NMOSD: 1.66 ± 0.98	NMOSD: 114.24 ± 221.04	NMOSD: 10.43 ± 10.71	–	–	–	–
	–		MS: 1.57 ± 1.30	MS: 71.55 ± 101.09	MS: 3.43 ± 6.0	–	–	–	–
	–		CTL: 1.10 ± 0.56	CTL: 25.68 ± 25.28	CTL: 1.71 ± 3.71	–	–	–	–
(Akiyuki Uzawa, 2009) [29]	–	CSF	–	NMOSD: 281.0 ± 212.4	–	–	–	–	–
	–		–	MS: 3.0 ± 0	–	–	–	–	–
	–		–	CTL: 3.1 ± 0.1	–	–	–	–	–
(K. Yanagawa, 2009) [30]	–	CSF	NMO(MY): 2.59 ± 0.55	NMO(MY): 59.74 ± 43.90	–	–	–	–	–
	–		NMOSD: 3.28 ± 0.87	NMOSD: 276.80 ± 273.19	–	–	–	–	–
	–		MS: 2.01 ± 1.48	MS: 42.05 ± 31.99	–	–	–	–	–
(Sema Icoz, 2010) [31]	–	CSF	–	NMOSD: 425.25 ± 99.67	–	–	–	–	–
	–		–	MS: 9.97 ± 0	–	–	–	–	–
	–		–	CTL: 6.64 ± 0	–	–	–	–	–
		Serum	–	NMOSD: 29.9 ± 6.64	–	–	–	–	–
			–	MS: 6.64 ± 0	–	–	–	–	–
			–	CTL: 4.98 ± 0	–	–	–	–	–
(Akiyuki Uzawa, 2010) [32]	–	CSF	NMOSD: 2.56 ± 7.40	NMOSD: 757.3 ± 1179.6	NMOSD: 3.72 ± 0	–	–	–	–
	–		MS: 1.08 ± 0	MS: 3.78 ± 5.08	MS: 3.72 ± 0	–	–	–	–
	–		CTL: 1.08 ± 0	CTL: 2.80 ± 1.57	CTL: 3.72 ± 0	–	–	–	–
		Serum	–	NMOSD: 0.98 ± 0.991	–	–	–	–	–
			–	CTL: 0.31 ± 0.45	–	–	–	–	–
(Ying Li, 2011) [33]	NMOSD: 2.53 ± 0.92	Serum	–	–	NMOSD: 74.06 ± 47.28	–	–	NMOSD: 76.14 ± 30.67	–
	MS: 1.88 ± 0.68		–	–	MS: 28.69 ± 8.04	–	–	MS: 65.97 ± 16.51	–
	CTL: 0.98 ± 0.42		–	–	CTL: 17.56 ± 6.79	–	–	CTL: 41.01 ± 8.95	–
(H.H. Wang, 2011) [34]	NMOSD: 3.72 ± 1.40	Serum	–	NMOSD: 17.90 ± 4.03	NMOSD: 58.07 ± 25.18	NMOSD: 111.75 ± 50.0	–	NMOSD: 64.89 ± 19.32	NMOSD: 30.15 ± 9.19
	MS: 2.58 ± 1.05		–	MS: 17.48 ± 3.50	MS: 30.67 ± 8.52	MS: 61.15 ± 24.48	–	MS: 56.82 ± 10.68	MS: 35.04 ± 9.88
	CTL: 1.36 ± 0.45		–	CTL: 14.83 ± 4.34	CTL: 13.95 ± 1.48	CTL: 36.39 ± 13.83	–	CTL: 33.13 ± 6.61	CTL: 35.16 ± 9.87
(Canan Ulusoy, 2012) [35]	–	Serum	–	–	NMOSD: 6.46 ± 1.98	–	–	NMOSD: 89.52 ± 16.9	NMOSD: 12.72 ± 3.57
	–		–	–	CTL: 8.11 ± 3.29	–	–	CTL: 74.90 ± 31.48	CTL: 8.72 ± 7.33
(K.-C. WANG, 2012) [36]	–	Serum	–	–	NMOSD: 25.38 ± 14.77	–	–	–	–
	–		–	–	MS: 0	–	–	–	–
(Aimin Wu, 2012) [37]	–	CSF	–	–	–	NMOSD: 99.95 ± 31.98	–	–	–
	–		–	–	–	MS: 93.45 ± 43.17	–	–	–
	–		–	–	–	CTL: 71.18 ± 32.68	–	–	–
(Takuya Matsushita, 2013) [38]	–	CSF	–	NMOSD: 616.19 ± 879.94	NMOSD: 1.97 ± 1.34	–	–	–	–
	–		–	MS: 0	MS: 0.85 ± 0.87	–	–	–	–
	–		–	CTL: 0	CTL: 0.77 ± 0.92	–	–	–	–
(B.D. Michael, 2013) [39]	–	Serum	–	NMOSD: 10.03 ± 18.88	NMOSD: 0.09 ± 0.06	–	–	–	–
	–		–	MS: 12.90 ± 18.31	MS: 0.03 ± 0.02	–	–	–	–
(Akiyuki Uzawa, 2013) [40]	–	CSF	–	NMOSD: 838.9 ± 2715.4	–	–	–	–	–
	–		–	MS: 3.0 ± 1.1	–	–	–	–	–
	–		–	CTL: 2.3 ± 1.1	–	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Study	% of Th17 cells	Sample for cytokines	IL-1β (pg/ml)	IL-6 (pg/ml)	IL-17 (pg/ml)	IL-21 (pg/ml)	IL-22 (pg/ml)	IL-23 (pg/ml)	TGF-β (pg/ml)
(Honghao Wang, 2013) [27]	–	Plasma	–	NMOSD: 13.48 ± 6.47	NMOSD: 12.79 ± 7.84	–	–	–	–
	–		–	MS: 11.45 ± 5.37	MS: 8.44 ± 3.02	–	–	–	–
	–		–	CTL:10.32 ± 5.36	CTL: 7.55 ± 2.67	–	–	–	–
(Honghao Wang, 2013) [41]	–	CSF	–	NMOSD: 24.95 ± 25.57	NMOSD: 18.56 ± 7.55	–	–	–	–
	–		–	MS: 10.73 ± 11.25	MS: 12.97 ± 4.37	–	–	–	–
	–		–	CTL: 7.99 ± 3.57	CTL: 11.45 ± 2.85	–	–	–	–
(Kai Chen Wang, 2013) [42]	–	Serum	–	NMOSD: 6.64 ± 7.98	NMOSD: 30.85 ± 31.85	–	–	–	–
	–		–	MS: 7.45 ± 10.82	MS: 33.71 ± 37.33	–	–	–	–
	–		–	CTL: 1.36 ± 0.75	CTL: 2.71 ± 1.48	–	–	–	–
(Wen Xu, 2013) [43]	NMOSD: 1.21 ± 0.74	Serum	–	NMOSD: 17.58 ± 4.31	–	NMOSD: 94.81 ± 37.16	NMOSD: 43.54 ± 32.90	–	–
	MS: 1.04 ± 0.71		–	MS: 15.72 ± 3.14	–	MS: 95.60 ± 31.30	MS: 41.55 ± 13.51	–	–
	CTL: 0.79 ± 0.57		–	CTL: 14.91 ± 2.97	–	CTL: 75.08 ± 24.85	CTL: 18.92 ± 6.52	–	–
(Philippe Horellou, 2015) [44]	–	CSF	–	NMOSD: 66.3 ± 23.7	–	–	–	–	–
	–		–	MS: 14.8 ± 9.4	–	–	–	–	–
	–		–	CTL: 2.2 ± 1.0	–	–	–	–	–
(Kunihiro Ichinose, 2015) [45]	–	CSF	–	–	NMOSD: 8.88 ± 4.19	–		–	–
	–		–	–	MS: 11.80 ± 2.65	–		–	–
(Yu-Jing Li, 2015) [46]	–	Serum	–	NMOSD: 15.06 ± 10.42	NMOSD: 78.11 ± 1.04	NMOSD: 249.81 ± 145.62	–	–	–
	–		–	MS: 7.36 ± 1.61	MS: 77.53 ± 0.78	MS: 131.35 ± 57.46	–	–	–
	–		–	CTL: 7.97 ± 1.59	CTL: 76.42 ± 0.31	CTL: 64.38 ± 27.07	–	–	–
(Fumitaka Shimizu1, 2015) [47]	–	Serum	NMOSD: 1.50 ± 1.23	NMOSD: 68.21 ± 24.6	–	–	–	–	–
	–		MS: 1.72 ± 0.26	MS: 52.2 ± 14.0	–	–	–	–	–
	–		CTL: 1.74 ± 0.30	CTL: 49.5 ± 12.2	–	–	–	–	–
(P. O. Barros, 2016) [48]	–	Plasma	NMOSD: 28.96 ± 11.16	NMOSD: 77.04 ± 29.31	NMOSD: 10.46 ± 8.85	–		NMOSD: 13.21 ± 12.55	–
	–		CTL: 8.42 ± 8.38	CTL: 14.18 ± 10.23	CTL: 8.08 ± 7.90	–		CTL: 9.88 ± 7.90	–
(Xueli Fan, 2016) [49]	–	Plasma	–	–	–	NMOSD: 253.64 ± 87.74	–	–	–
	–		–	–	–	CTL: 176.28 ± 42.38	–	–	–
	–	CSF	–	–	–	NMOSD: 294.76 ± 72.77	–	–	–
	–		–	–	–	CTL: 210.43 ± 42.35	–	–	–
(Kimitoshi Kimura, 2016) [50]	NMOSD: 8.57 ± 5.71	–	–	–	–	–	–	–	–
	MS: 8.21 ± 5.54		–	–	–	–	–	–	–
	CTL: 8.75 ± 3.21		–	–	–	–	–	–	–
(Yuge Wang, 2016) [51]	–	CSF	–	NMOSD: 9.52 ± 4.66	NMOSD: 14.3 ± 9.18	–	–	–	–
	–		–	MS: 7.76 ± 2.54	MS: 11.32 ± 2.64	–	–	–	–
	–		–	CTL: 7.89 ± 0.57	CTL: 8.00 ± 8.76	–	–	–	–
(Tao Yang, 2016) [52]	–	Plasma	NMOSD: 22.25 ± 10.05	–	–	–	–	–	–
	–		MS: 18.81 ± 11.63	–	–	–	–	–	–
	–		CTL: 12.49 ± 9.35	–	–	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Study	% of Th17 cells	Sample for cytokines	IL-1β (pg/ml)	IL-6 (pg/ml)	IL-17 (pg/ml)	IL-21 (pg/ml)	IL-22 (pg/ml)	IL-23 (pg/ml)	TGF-β (pg/ml)
(Qiuming Zeng, 2016) [53]	–	Plasma	NMOSD: 28.21 ± 9.02	–	–	–	–	–	–
	–		CTL: 5.79 ± 2.50	–	–	–	–	–	–
	–	CSF	NMOSD: 13.58 ± 3.06	–	–	–	–	–	–
	–		CTL: 5.53 ± 2.04	–	–	–	–	–	–
(Priscila O. Barros, 2017) [22]	–	Plasma	NMOSD: 60.98 ± 53.66	NMOSD: 146.34 ± 85.37	NMOSD: 60.98 ± 34.15	–	–	–	–
	–		CTL: 19.51 ± 19.51	CTL: 31.71 ± 29.27	CTL: 4.88 ± 14.63	–	–	–	–
(Akio Kimura, 2017) [24]	–	CSF	–	NMOSD: 706 ± 1570	–	–	–	–	–
	–		–	MS: 4.65 ± 9.15	–	–	–	–	–
	–		–	–	–	–	–	–	–
(Tomohiko Uchida, 2017) [4]	–	CSF	NMOSD: 0.49 ± 0	NMOSD: 89.3 ± 737.3	NMOSD: 2.96 ± 12.15	NMOSD: 142.0 ± 0	NMOSD: 9.37 ± 0	NMOSD: 13.0 ± 13.8	–
	–		MS: 0.49 ± 0	MS: 59.1 ± 43.4	MS: 40.58 ± 43.08	MS: 141.7 ± 0	MS: 9.37 ± 0	MS: 13.0 ± 43.1	–
	–		CTL: 0.49 ± 0	CTL: 46.9 ± 52.8	CTL: 2.96 ± 15.16	CTL: 141.7 ± 0	CTL: 9.37 ± 0	CTL: 13.0 ± 0	–
		Serum	–	NMOSD: 2.32 ± 0	NMOSD: 3.22 ± 0	–	–	–	–
			–	MS: 2.32 ± 0	MS: 3.22 ± 0	–	–	–	–
			–	CTL: 2.32 ± 76.12	CTL: 3.22 ± 0	–	–	–	–
(Akiyuki Uzawa, 2017) [5]	–	CSF	–	NMOSD: 23.5 ± 2814.92	–	–	–	–	–
	–		–	MS: 3.5 ± 2.97	–	–	–	–	–
	–		–	CTL: 6.6 ± 62,063.1	–	–	–	–	–
(Cong Zhao, 2017) [23]	–	Plasma	–	NMOSD: 17.09 ± 17	–	NMOSD: 17.80 ± 12.50	–	–	–
	–		–	CTL: 9.53 ± 6.02	–	CTL: 10.38 ± 3.66	–	–	–
(Ryotaro Ikeguchi, 2018) [20]	–	CSF	–	NMOSD: 6.1 ± 7.0	–	–		–	–
	–		–	MS: 1.8 ± 0.48	–	–		–	–
(Shanshan Pei, 2018) [21]	–	CSF	–	NMOSD: 10.62 ± 7.97	NMOSD: 9.73 ± 9.54	–	–	–	–
	–		–	MS: 5.69 ± 2.67	MS: 5.75 ± 3.75	–	–	–	–
	–		–	CTL: 2.53 ± 0.43	CTL: 3.84 ± 1.86	–	–	–	–
(Nanping Ai, 2019) [19]	–	Serum	–	–	NMOSD: 9.93 ± 0.25	–	–	–	–
	–		–	–	CTL: 10.55 ± 0.82	–	–	–	–
(Baozhu Liu, 2019) [18]	–	CSF	NMOSD: 1.71 ± 1.45	NMOSD: 11.30 ± 19.76	–	–	–	–	–
	–		MS: 1.53 ± 0.93	MS: 7.18 ± 7.01	–	–	–	–	–
	–		CTL: 0.72 ± 0.33	CTL: 5.74 ± 1.74	–	–	–	–	–
(Clarice Monteiro, 2019) [17]	–	Plasma	–	NMOSD: 117.50 ± 66	NMOSD: 44.53 ± 42.2	NMOSD: 26.59 ± 21.5	–	–	–
	–		–	CTL: 12.44 ± 30.91	CTL: 1.91 ± 2.75	CTL: 2.38 ± 2.74	–	–	–
(Yuzhen Wei, 2019) [3]	–	Serum	–	NMOSD: 9.23 ± 21.1	NMOSD: 8.92 ± 15.9	–	–	NMOSD: 349.08 ± 938	NMOSD: 24.68 ± 13.9
	–		–	MS: 2.7 ± 3.1	MS: 12.2 ± 14.2	–	–	MS: 333.6 ± 400.5	MS: 24.1 ± 5.0
	–		–	CTL: 2.5 ± 1.6	CTL: 5.2 ± 3.9	–	–	CTL: 59.1 ± 68.2	CTL: 14.9 ± 7.5

NMOSD: neuromyelitis optica spectrum disorders; MS: multiple sclerosis; CSF: Cerebrospinal fluid; CTL: Control group; HC: Healthy controls.

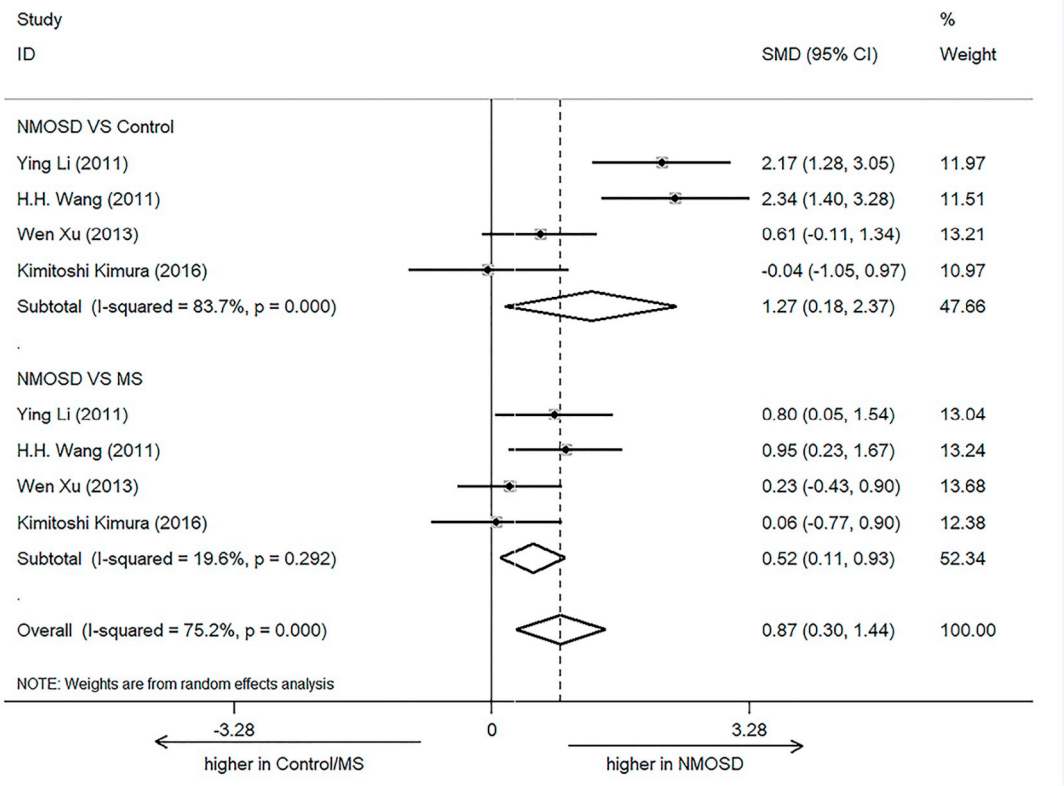


Fig. 2. Forest plot of the proportion of Th17 cells.

publication bias detection.

3.3. The level of Th17 related cytokines

3.3.1. IL6

Twenty-three included studies compared the level of IL6 between NMOSD patients and a control group. The results showed that the level of IL6 was higher in NMOSD patients than in the control subjects [0.94, (0.65, 1.23), $P < 0.001$] (Fig. 3a). Specifically, the level of IL6 in CSF was higher in NMOSD patients than in the control subjects in CSF [0.83, (0.39, 1.26), $P < 0.001$], plasma [1.51, (0.66, 2.36), $P < 0.001$], and serum [0.77, (0.53, 1.01), $P < 0.001$] (Fig. 3a). The heterogeneity among studies was high (I^2 79.3%, $P < 0.05$); therefore, REM was considered. We performed the funnel plot (Fig. S1a) and publication bias detection. Begg's and Egger's tests indicated a publication bias ($P = 0.002$, $P < 0.001$, Fig. S2a), and the trim-and-fill test revealed that the publication bias of studies did not impact the estimates. Sensitivity analysis indicated that the results of studies were robust (Fig. S3a).

Twenty-one included studies reported the level of IL6 between NMOSD patients and MS patients. The results showed that the level of IL6 was higher in NMOSD patients than in MS patients [0.51, (0.29, 0.73), $P < 0.001$] (Fig. 3b); specifically, in CSF [0.63, (0.32, 0.94), $P < 0.001$] and serum [0.32, (0.00, 0.64), $P = 0.049$] (Fig. 3b). There was only one study reporting the level of IL6 in plasma [27]. The heterogeneity among studies was high (I^2 63.7%, $P < 0.05$), and REM was considered. We performed the funnel plot (Fig. S1b) and publication bias detection. Begg's and Egger's tests indicated there was no publication bias ($P = 0.264$, $P = 0.1$, Fig. S2b), and the sensitivity analysis indicated that the results of studies were robust (Fig. S3b).

3.3.2. IL17

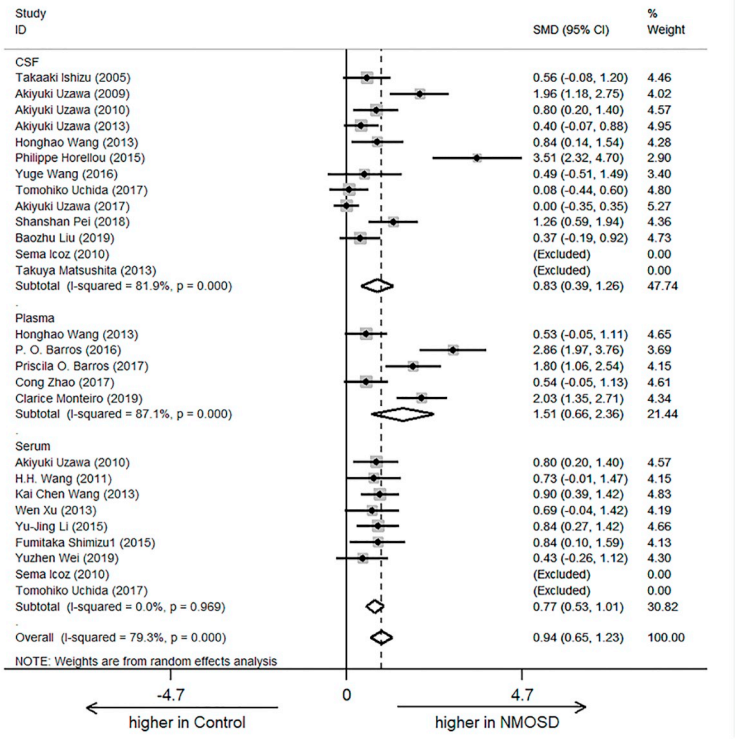
Seventeen included studies reported the level of IL17 between NMOSD patients and control group. The results showed that the level of IL17 was higher in NMOSD patients than in the control subjects [0.87, (0.42, 1.33), $P < 0.001$] (Fig. 4a). The heterogeneity among studies was high (I^2 87.3%, $P < 0.05$), and we considered the REM. The level of IL17 in the CSF was higher in NMOSD patients than in control subjects in CSF [0.76, (0.35, 1.16), $P < 0.001$] and plasma [1.15, (0.43, 1.87), $P = 0.002$]. Results showed no significant difference in the serum [0.81, (−0.20, 1.83), $P = 0.118$] (Fig. 4a). Begg's and Egger's tests indicated there was no publication bias ($P = 0.091$, $P = 0.079$), sensitivity analysis indicated that the results of studies were robust.

Fourteen included studies reported the level of IL17 between NMOSD patients and MS patients. The results showed that the level of IL17 was higher in NMOSD patients than in MS patients [0.47, (0.03, 0.90), $P = 0.036$] (Fig. 4b), with a significant increase observed in the serum IL17 levels [0.70, (0.12, 1.29), $P = 0.036$] (Fig. 4b). Results showed no significant difference in the CSF IL17 levels [0.23, (−0.49, 0.95), $P = 0.538$] (Fig. 4b). Only one study reporting the level of IL17 in plasma of NMSOD and MS patients was obtained [27]. The heterogeneity among studies was high (I^2 83.3%, $P < 0.05$), and REM was considered. Begg's and Egger's tests indicated there was no publication bias ($P = 0.274$, $P = 0.221$), sensitivity analysis indicated that the results of studies were robust.

3.3.3. IL21

Eight included studies reported the level of IL21 between NMOSD patients and the control group. The results showed that the level of IL21 in the serum was higher in NMOSD patients was higher than in the control subjects [1.40, (0.57, 2.23), $P = 0.001$] (Fig. 5a). The heterogeneity among studies was high (I^2 73.2%, < 0.05), and REM was considered. The level of IL21 in the CSF [1.04, (0.48, 1.59), $P < 0.001$]

a



b

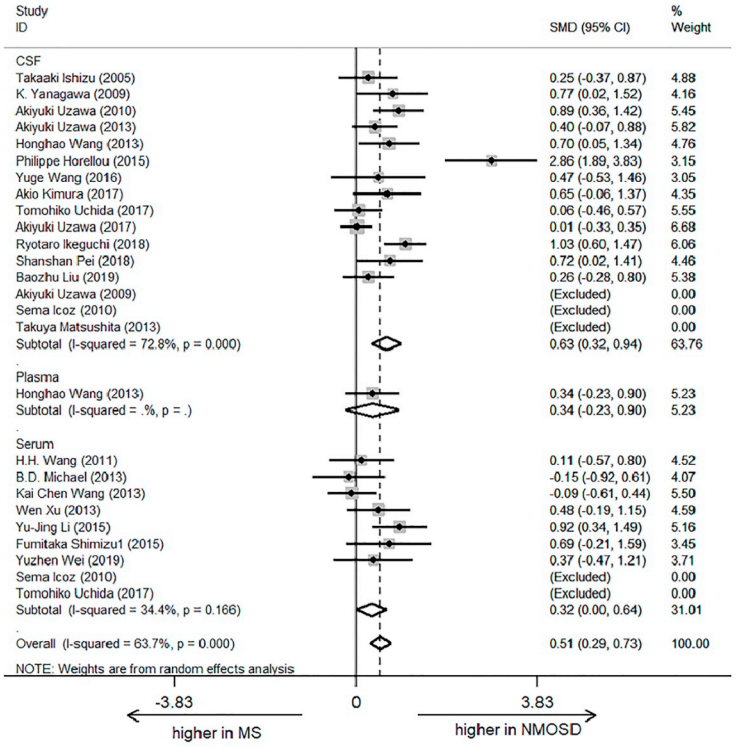
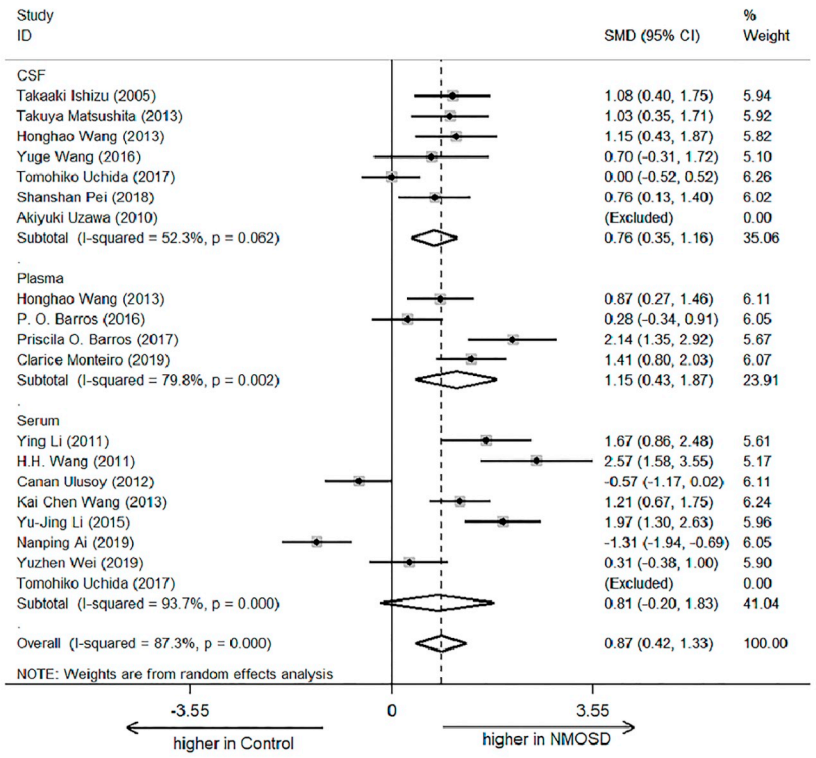


Fig. 3. Forest plot of the level of IL6. **a** NMOSD patients vs control group; **b** NMOSD patients vs MS patients.

a



b

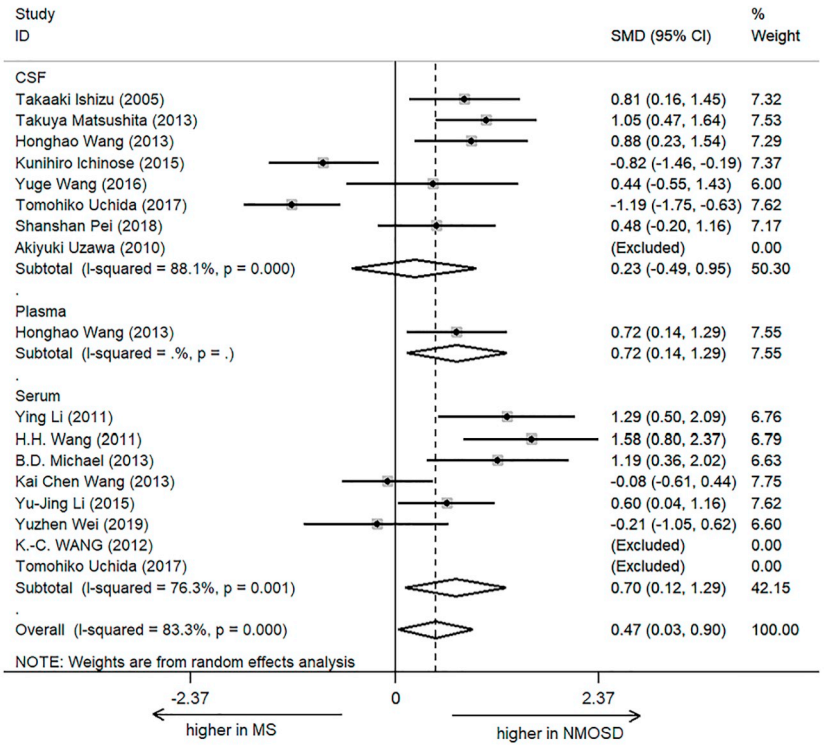
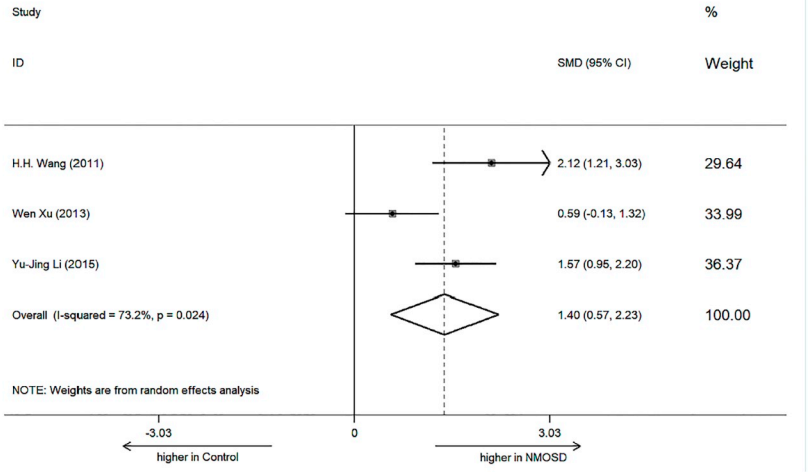
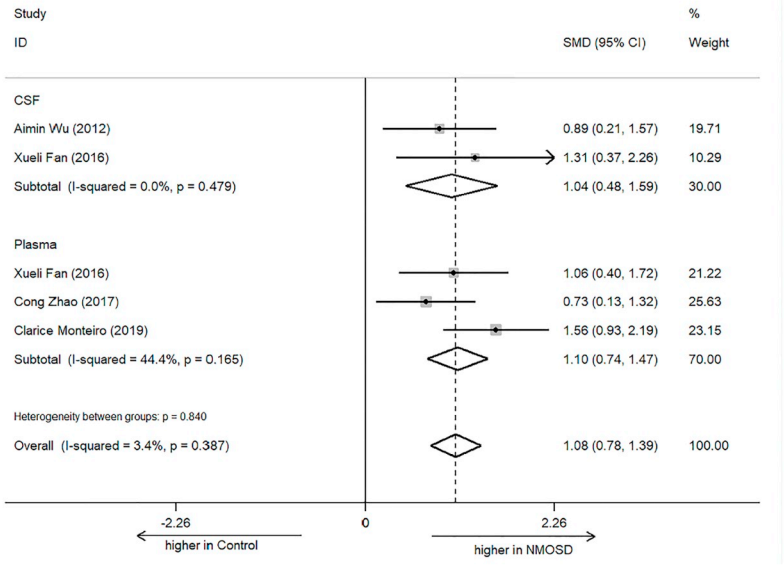


Fig. 4. Forest plot of the level of IL17. **a** NMOSD patients vs control group; **b** NMOSD patients vs MS patients.

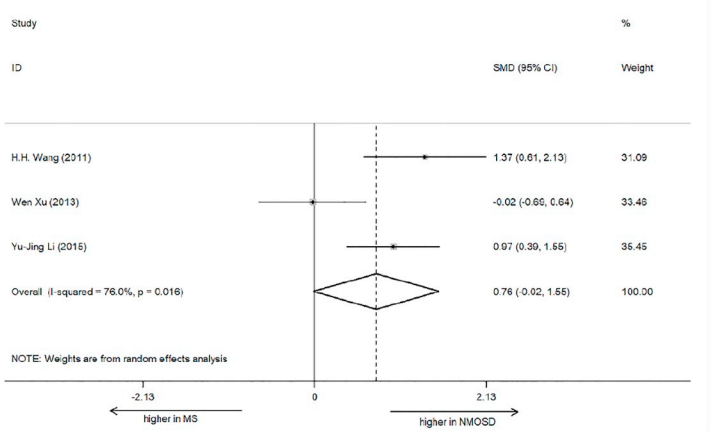
a



b



c



(caption on next page)

Fig. 5. Forest plot of the level of IL21. a IL21in serum between NMOSD patients and control group; b IL21 in CSF and plasma between NMOSD patients and control group; c IL21 in serum between NMOSD patients and MS patients.

and plasma [1.10, (0.74, 1.47), $P < 0.001$] was higher in NMOSD patients than in control subjects (Fig. 5b). The heterogeneity among studies was low ($I^2 = 0\%$, $P = 0.479$; $I^2 = 44.4\%$, $P = 0.165$), and FEM was considered.

Three included studies reported the level of IL21 in serum between NMOSD patients and MS patients, but the results showed no significant difference between the two groups [0.76, (−0.02, 1.55), $P = 0.056$] (Fig. 5c).

3.3.4. IL1β

Eight included studies reported the level of IL1β between NMOSD patients and the control group. The level of IL1β in CSF [1.38, (0.32, 2.44), $P = 0.01$] and plasma [1.75, (0.86, 2.64), $P < 0.001$] was higher in NMOSD patients than in control subjects (Fig. 6a). The heterogeneity among studies was high (I^2 85.4%, $P < 0.05$), the REM was considered.

Three included studies reported the level of IL1β in CSF between NMOSD patients and MS patients, and no significant difference was observed between the groups [0.28, (−0.08, 0.64), $P = 0.130$] (Fig. 6b). The heterogeneity among studies was low (I^2 26.2%, $P = 0.258$), FEM was considered.

3.3.5. IL23

Four included studies reported the level of IL23 in serum between NMOSD patients and control group. The result showed a higher level of serum IL23 in NMOSD patients than in control subjects [1.14, (0.34, 1.94), $P = 0.005$] (Fig. 7a). The heterogeneity among studies was high (I^2 78.5%, $P = 0.03$), and REM was considered.

Three included studies reported the level of IL23 in serum between NMOSD patients and MS patients. The result showed no significant difference between groups [0.36, (−0.07, 0.79), $P = 0.105$] (Fig. 7b). The heterogeneity among studies was low (I^2 0%, $P = 0.628$), and FEM was considered.

3.3.6. TGFβ

Three included studies reported the level of TGFβ in serum between NMOSD patients and control group. Result showed no significant difference between groups [0.34, (−0.46, 1.14), $P = 0.411$] (Fig. 7a). The heterogeneity among studies was high (I^2 75.9%, $P = 0.016$), and REM was considered.

Two included studies reported the level of TGFβ in serum between NMOSD patients and MS patients. No significant difference was observed between groups [−0.28, (−0.81, 0.25), $P = 0.1302$] (Fig. 7b). The heterogeneity among studies was low (I^2 1.5%, $P = 0.314$), and FEM was considered.

4. Discussion

Neuromyelitis optica (NMO) was first proposed by Devic in 1894, who called it 'Devic disease,' and was considered as a variant of MS, and has been developed ever since. In 1999, after summing up the clinical data of patients, Wingerchuk et al. [54] found that divided NMO into single-phase type NMO and recurrent-type NMO according to the course of the disease, based on which the diagnostic criteria of NMO were first developed. Lennon et al. [55] discovered high concentrations of specific AQP4 antibodies in the serum of NMO patients in 2004 and identified NMO as a distinct disease entity independent of MS. In 2006, Wingerchuk et al. [56] developed the NMO diagnostic criteria further, incorporating the result of AQP4 antibodies in serum. On this basis, Wingerchuk et al. [57] proposed the concept of NMO spectrum in 2007, including NMO and NMO related diseases. In 2015, Wingerchuk et al. [58] proposed a unified concept of NMOSD and developed the new diagnostic criteria, which has far-reaching implications for clinical diagnosis and treatment of NMOSD.

In addition to anti-AQP4 antibodies, several other molecular biomarkers were studied to help elucidate the immune pathogenesis of NMOSD [6]. These findings have deepened our understanding of the pathogenesis of NMOSD and provided essential guidance for the development of novel therapeutic approaches. A growing number of immunological studies have reported the cytokines and chemokines to play a vital role in the pathogenesis of NMOSD [59] and indicates that NMOSD is a Th2- and Th17-dominant disease. Th2-related cytokines and chemokines such as IL13 are upregulated in the CSF of NMOSD patients [59]; besides, IL-25, IL-31, and IL-33 are recently found Th2-related cytokines in NMOSD. Th17-associated cytokines, might, therefore, may be a key player in NMOSD inflammation [59]. The results of related researches are still ambiguous about the proportion of Th17 cells and the level of Th17-related cytokines in NMOSD patients; therefore, we conducted this meta-analysis.

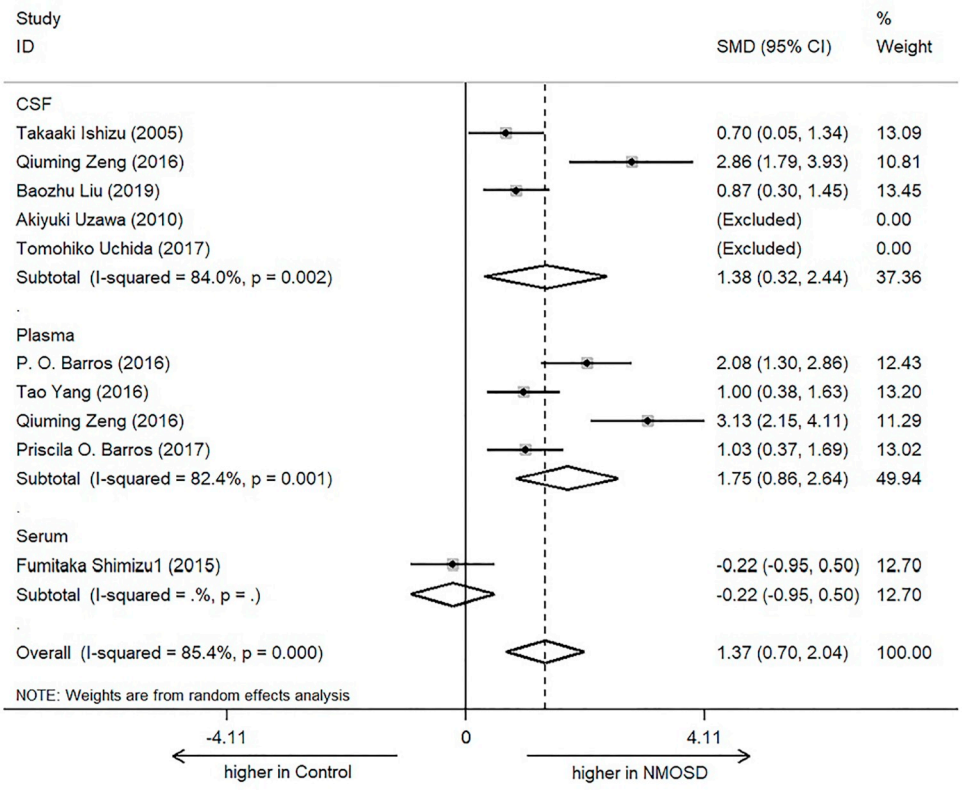
Our results revealed that, the proportion of Th17 cells and the levels of Th17-related cytokines such as IL6, IL17, IL1β, and IL21 in CSF and plasma, and IL6, IL21, and IL23 in serum were higher in NMOSD patients than in control subjects, suggesting the role of Th17 cells and Th17-related cytokines play an important role in the immune pathogenesis of NMOSD. Therefore, combined with drugs for AQP4 antibody, interventions targeting Th17 cells and cytokines IL6, IL17, IL1β, IL21, and IL23 might significantly improve the treatment effect, reduce the severity of the disease, improve the prognosis, and reduce or prevent recurrence in NMOSD patients. Considering that NMOSD and MS have some similarities, we also analyzed the proportion of Th17 cells and the levels of Th17-related cytokines between the NMOSD patients and MS patients. The results showed that the proportion of Th17 cells and the levels of IL6 in CSF and serum and IL17 in plasma and serum were higher in NMOSD patients than in MS patients.

In addition to the anti-AQP4 antibody, other biomarkers involved in Th17 cells and astrocytic damages for NMOSD have also been reported. For example, IL-6 in PB is associated with the production of anti-AQP4 antibody. Since these two antibodies have been found to play an essential role in the pathogenesis of NMOSD, the treatment of NMOSD patients in recent years has mainly focused on the depletion of autoantibodies and suppression of lymphocytes, such as AQP4-IgG and IL6R-IgG (tocilizumab). In addition to this, complement-targeting therapy, including eculizumab and C1 inhibitor, has recently been studied in NMOSD patients. Based on the results of this study, we hypothesized that in addition to AQP4-IgG, complement and IL-6R are of great significance in NMOSD, Th17 cells and Th17-related cytokines might also play a role in the diagnosis and treatment of NMOSD.

In our study, we observed differences in the basic characteristics of the included patients between groups. For example, the percent of female patients was higher in NMOSD than the control group and MS patients, which is consistent with epidemiological data. NMOSD patients were older, with higher EDSS scores than those of MS patients. These results are also consistent with the survey results of clinical patients.

This study has several apparent deficiencies and limitations. Firstly, the heterogeneities of several outcomes were high. As shown in Table 1, the types of control group mainly included healthy controls (HC), other neurological diseases (OND) and other non-inflammatory neurological diseases (ONNDs). The countries mainly included China, Japan, France, and others. We conducted a subgroup analysis of the types of control group and countries, and the results showed a decrease in heterogeneities (data not shown). Additionally, inconsistencies among studies, such as the duration of the disease and EDSS scores of NMOSD, sampling time, and different testing methods and standards, all might

a



b

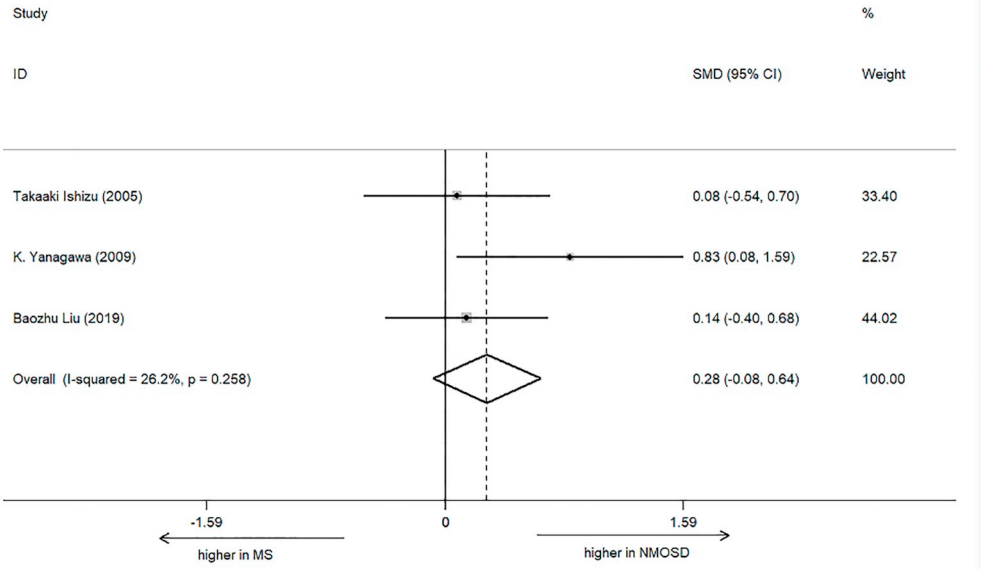


Fig. 6. Forest plot of the level of IL1β. **a** NMOSD patients vs control group; **b** IL1β in CSF between NMOSD patients and MS patients.

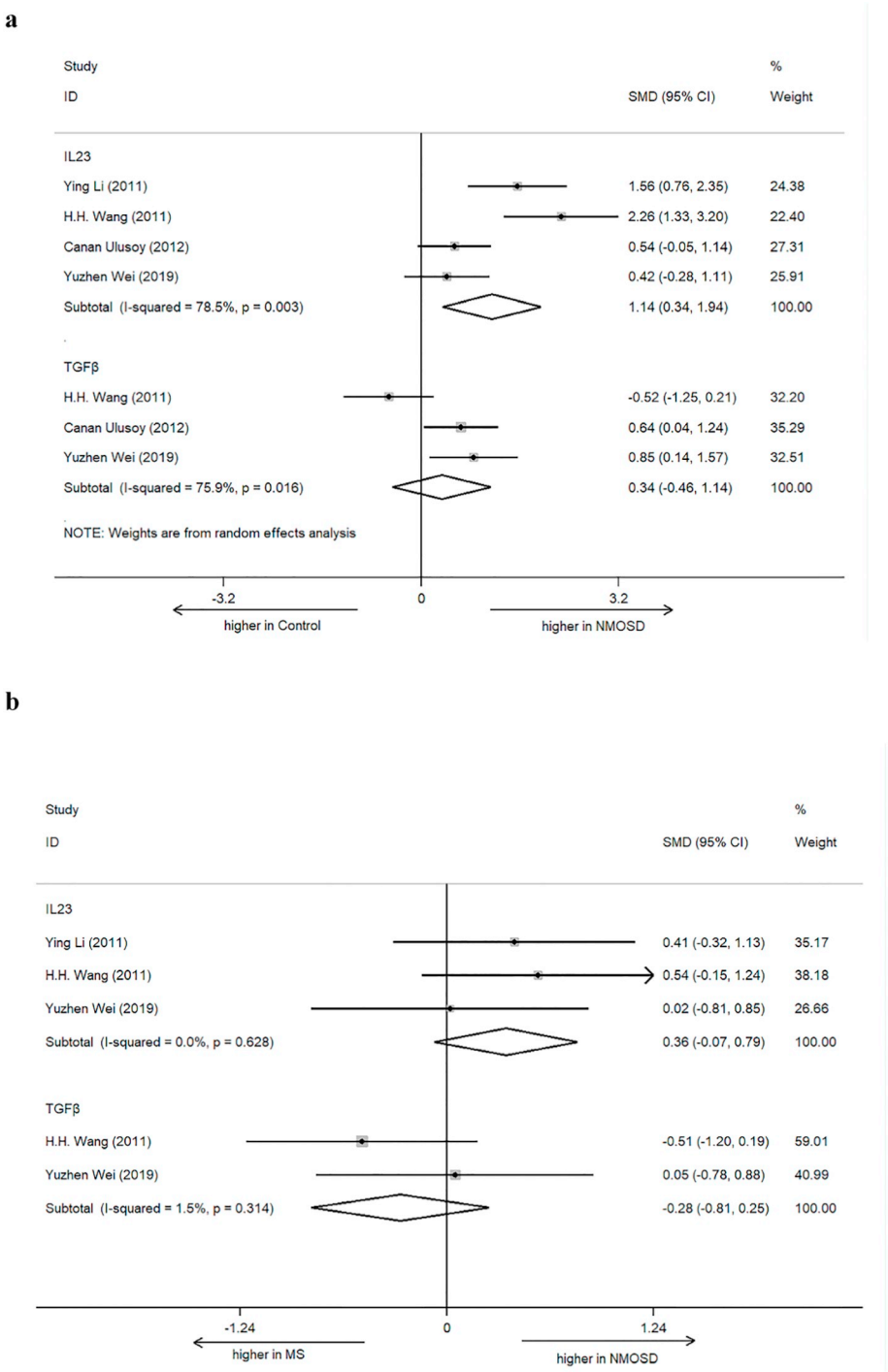


Fig. 7. Forest plot of the levels of IL23 and TGFβ in serum. **a** NMOSD patients vs control group; **b** NMOSD patients vs MS patients.

have led to the heterogeneity. Secondly, the levels of several cytokines such as IL21 in plasma of MS patients, IL22, IL23, and TGFβ in CSF and serum, had no one or merely one related article, and the results could not be meta-analyzed. Finally, we did not analyze the AQP4-IgG serostatus in the NMOSD group, nor did we verify the differences of Th17 cells and related cytokine levels between the relapse phase and remission phase of NMOSD. Therefore, it cannot be concluded that Th17 cells and proinflammatory cytokines might be relevant biomarkers of disease activity in NMOSD, which we will continue to analyze in our future studies with an increasing number of related researches.

5. Conclusion

The current meta-analysis demonstrated that the proportion of Th17 cells was higher in NMOSD patients than in control subjects and MS patients. The levels of Th17-related cytokines in NMOSD patients, especially IL6, IL17, IL1β, IL21, and IL23, were higher in NMOSD patients than the control group. The levels of IL6 and IL17 were higher in NMOSD patients than in MS patients. The results of levels of cytokines were different according to the type of biological samples such as CSF, plasma, and serum. Further research, including studies with large sample size and longer follow-up periods, are required to study in-depth the immune mechanism of NMOSD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105793.

Funding sources

This work was support by the Shanxi Graduate Education Innovation Project (No. 2018BY070) and the International Scientific and Technological Cooperation Project (No. 201703D421018).

Declaration of competing interest

All authors have no conflicts of interest to disclose.

References

[1] D.M. Wingerchuk, B. Banwell, J.L. Bennett, P. Cabre, W. Carroll, T. Chitnis, J. de Seze, K. Fujihara, B. Greenberg, A. Jacob, S. Jarius, M. Lana-Peixoto, M. Levy, J.H. Simon, S. Tenembaum, A.L. Traboulsee, P. Waters, K.E. Wellik, B.G. Weinshenker, International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85 (2) (2015) 177–189, https://doi.org/10.1212/WNL.0000000000001729.

[2] Bradl M, Misu T, Takahashi T, Watanabe M, Mader S, Reindl M, Adzemovic M, Bauer J, Berger T, Fujihara K, Itoyama Y, Lassmann H(2009)Neuromyelitis optica: Pathogenicity of patient immunoglobulin in vivo.ANN NEUROL 66 (5):630–643. 'doi:'https://doi.org/10.1002/ana.21837

[3] Wei Y, Chang H, Li X, Wang H, Du L., Zhou H, Xu W, Ma Y, Yin L, Zhang X (2019) Cytokines and Tissue Damage Biomarkers in First-Onset Neuromyelitis Optica Spectrum Disorders: Significance of Interleukin-6. NEUROIMMUNOMODULAT 25 (4):215–224. 'doi:'https://doi.org/10.1159/000494976

[4] Uchida T, Mori M, Uzawa A, Masuda H, Muto M, Ohtani R, Kuwabara S(2017) Increased cerebrospinal fluid metalloproteinase-2 and interleukin-6 are associated with albumin quotient in neuromyelitis optica: Their possible role on blood–brain barrier disruption.MULT SCLER J 23 (8):1072–1084. 'doi:'https://doi.org/10.1177/1352458516672015

[5] Uzawa A, Mori M, Masuda H, Ohtani R, Uchida T, Sawai S, Kuwabara S(2017) Interleukin-6 analysis of 572 consecutive CSF samples from neurological disorders: A special focus on neuromyelitis optica.CLIN CHIM ACTA 469:144–149. 'doi:'https://doi.org/10.1016/j.cca.2017.03.006

[6] Chang KH, Ro LS, Lyu RK, Chen CM(2015)Biomarkers for neuromyelitis optica. CLIN CHIM ACTA 440:64–71. 'doi:'https://doi.org/10.1016/j.cca.2014.11.004

[7] Korn T, Bettelli E, Oukka M, Kuchroo VK(2009)IL-17 and Th17 Cells.ANNU REV IMMUNOL 27:485–517. 'doi:'https://doi.org/10.1146/annurev.immunol.021908.132710

[8] Kishimoto T(2005)Interleukin-6: from basic science to medicine–40 years in immunology.ANNU REV IMMUNOL 23:1–21. 'doi:'https://doi.org/10.1146/annurev.immunol.23.021704.115806

[9] Murphy KM, Reiner SL(2002)The lineage decisions of helper T cells.NAT REV IMMUNOL 2 (12):933–944. 'doi:'https://doi.org/10.1038/nri954

[10] Korn T, Bettelli E, Oukka M, Kuchroo VK(2009)IL-17 and Th17 Cells. ANNU REV IMMUNOL 27:485–517. 'doi:'https://doi.org/10.1146/annurev.immunol.021908.132710

[11] Mitsdoerffer M, Kuchroo V, Korn T (2013) Immunology of neuromyelitis optica: a T cell-B cell collaboration. Ann N Y Acad Sci 1283 (1):57–66. 'doi:'https://doi.org/10.1111/nyas.12118

[12] Trenova AG, Slavov GS, Manova MG, Draganaova-Filipova MN, Mateva NG, Miteva LD, Stanilova SA (2017) Alterations in serum levels of IL-17 in contrast to TNF-alpha correspond to disease-modifying treatment in relapsing-remitting multiple sclerosis. Scand J Clin Lab Invest 77 (4):283–288. 'doi:'https://doi.org/10.1080/00365513.2017.1303843

[13] J.K. Kolls, A. Linden, Interleukin-17 family members and inflammation, IMMUNITY 21 (4) (2004) 467–476, https://doi.org/10.1016/j.immuni.2004.08.018.

[14] Beadling C, Slifka MK (2006) Regulation of innate and adaptive immune responses by the related cytokines IL-12, IL-23, and IL-27.Arch Immunol Ther Exp (Warsz) 54 (1):15–24. 'doi:'https://doi.org/10.1007/s00005-006-0002-6

[15] Segal BM (2010) Th17 cells in autoimmune demyelinating disease. SEMIN IMMUNOPATHOL 32 (1):71–77. 'doi:'https://doi.org/10.1007/s00281-009-0186-z.

[16] Y.F. Li, S.X. Zhang, X.W. Ma, Y.L. Xue, C. Gao, X.Y. Li, Levels of peripheral Th17 cells and serum Th17-related cytokines in patients with multiple sclerosis: a meta-analysis, Mult Scler Relat Disord 18 (2017) 20–25, https://doi.org/10.1016/j.msard.2017.09.003.

[17] Monteiro C, Fernandes G, Kasahara TM, Barros PO, Dias A, Araujo A, Ornelas A, Aguiar RS, Alvarenga R, Bento C (2019) The expansion of circulating IL-6 and IL-17-secreting follicular helper T cells is associated with neurological disabilities in neuromyelitis optica spectrum disorders. J NEUROIMMUNOL 330:12–18. 'doi:'https://doi.org/10.1016/j.jneuroim.2019.01.015

[18] B. Liu, X. Zhong, Z. Lu, W. Qiu, X. Hu, H. Wang, Cerebrospinal fluid level of soluble CD27 is associated with disease severity in neuromyelitis optica Spectrum disorder, NEUROIMMUNOMODULAT 25 (4) (2019) 185–192, https://doi.org/10.1159/000489561.

[19] Ai N, Liu H, Zhou H, Lin D, Wang J, Yang M, Song H, Sun M, Xu Q, Wei S (2019) Cytokines and chemokines expression in serum of patients with neuromyelitis optica. NEUROPSYCH DIS TREAT 15:303–310. 'doi:'https://doi.org/10.2147/NDT.S185336

[20] R. Ikeguchi, Y. Shimizu, S. Shimizu, K. Kitagawa, CSF and clinical data are useful in differentiating CNS inflammatory demyelinating disease from CNS lymphoma, Mult. Scler. 24 (9) (2018) 1212–1223, https://doi.org/10.1177/1352458517717804.

[21] Pei S, Zheng D, Wang Z, Hu X, Pan S, Wang H (2018) Elevated soluble syndecan-1 levels in neuromyelitis optica are associated with disease severity. CYTOKINE 111:140–145. 'doi:'https://doi.org/10.1016/j.cyto.2018.08.017

[22] Barros PO, Dias A, Kasahara TM, Ornelas A, Aguiar RS, Leon SA, Ruiz A, Marignier R, Araujo A, Alvarenga R, Bento C (2017) Expansion of IL-6(+) Th17-like cells expressing TLRs correlates with microbial translocation and neurological disabilities in NMOSD patients. J NEUROIMMUNOL 307:82–90. 'doi:'https://doi.org/10.1016/j.jneuroim.2017.04.001

[23] C. Zhao, H.Z. Li, D.D. Zhao, C. Ma, F. Wu, Y.N. Bai, M. Zhang, Z.Y. Li, J. Guo, Increased circulating T follicular helper cells are inhibited by rituximab in neuromyelitis optica spectrum disorder, Front. Neurol. 8 (2017) 104, https://doi.org/10.3389/fneur.2017.00104.

[24] Kimura A, Takemura M, Saito K, Serrero G, Yoshikura N, Hayashi Y, Inuzuka T(2017) Increased cerebrospinal fluid progranulin correlates with interleukin-6 in the acute phase of neuromyelitis optica spectrum disorder. J NEUROIMMUNOL 305:175–181. 'doi:'https://doi.org/10.1016/j.jneuroim.2017.01.006

[25] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Reprint–preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Phys. Ther. 89 (9) (2009) 873–880.

[26] Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. EUR J EPIDEMIOL 25 (9):603–605. 'doi:'https://doi.org/10.1007/s10654-010-9491-z.

[27] Wang H, Wang K, Wang C, Xu F, Qiu W, Hu X(2013)Increased plasma interleukin-32 expression in patients with neuromyelitis optica.J CLIN IMMUNOL 33 (3):666–670. 'doi:'https://doi.org/10.1007/s10875-012-9837-2

[28] Ishizu T, Osoegawa M, Mei FJ, Kikuchi H, Tanaka M, Takakura Y, Minohara M, Murai H, Mihara F, Taniwaki T, Kira J (2005) Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. BRAIN 128 (Pt 5):988–1002. 'doi:'https://doi.org/10.1093/brain/awh453

[29] Uzawa A, Mori M, Ito M, Uchida T, Hayakawa S, Masuda S, Kuwabara S (2009) Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. J NEUROL 256 (12):2082–2084. 'doi:'https://doi.org/10.1007/s00415-009-5274-4

[30] Yanagawa K, Kawachi I, Toyoshima Y, Yokoseki A, Arakawa M, Hasegawa A, Ito T, Kojima N, Koike R, Tanaka K, Kosaka T, Tan CF, Kakita A, Okamoto K, Tsujita M, Sakimura K, Takahashi H, Nishizawa M (2009) Pathologic and immunologic profiles of a limited form of neuromyelitis optica with myelitis. NEUROLOGY 73 (20):1628–1637. 'doi:'https://doi.org/10.1212/WNL.0b013e3181c1deb9

[31] Içöz S, Tüzün E, Kürtüncü M, Durmuş H, Mutlu M, Eraksoy M, Akman-Demir G(2010)Enhanced IL-6 production in aquaporin-4 antibody positive neuromyelitis optica patients.INT J NEUROSCI 120 (1):71–75. 'doi:'https://doi.org/10.3109/00207450903428970

[32] Uzawa A, Mori M, Arai K, Sato Y, Hayakawa S, Masuda S, Taniguchi J, Kuwabara S (2010) Cytokine and chemokine profiles in neuromyelitis optica: significance of interleukin-6. Mult Scler 16 (12):1443–1452. 'doi:'https://doi.org/10.1177/1352458510379247

[33] Li Y, Wang H, Long Y, Lu Z, Hu X(2011)Increased memory Th17 cells in patients with neuromyelitis optica and multiple sclerosis.J NEUROIMMUNOL 234 (1–2):155–160. 'doi:'10.1016/j.jneuroim.2011.03.009.

[34] Wang HH, Dai YQ, Qiu W, Lu ZQ, Peng FH, Wang YG, Bao J, Li Y, Hu XQ (2011) Interleukin-17-secreting T cells in neuromyelitis optica and multiple sclerosis during relapse. J CLIN NEUROSCI 18 (10):1313–1317. 'doi:'10.1016/j.jocn.2011.01.031.

[35] Ulusoy C, Tuzun E, Kurtuncu M, Turkoglu R, Akman-Demir G, Eraksoy M (2012) Comparison of the cytokine profiles of patients with neuronal-antibody-associated central nervous system disorders. INT J NEUROSCI 122 (6):284–289. 'doi:'https://doi.org/10.3109/00207454.2011.648762

[36] Wang KC, Tsai CP, Lee CL, Chen SY, Chin LT, Chen SJ(2012)Elevated plasma high-mobility group box 1 protein is a potential marker for neuromyelitis optica. NEUROSCIENCE 226:510–516. 'doi:'10.1016/j.neuroscience.2012.08.041.

[37] A. Wu, X. Zhong, H. Wang, W. Xu, C. Cheng, Y. Dai, J. Bao, W. Qiu, Z. Lu, X. Hu, Cerebrospinal fluid IL-21 levels in Neuromyelitis Optica and multiple sclerosis, CAN J NEUROL SCI 39 (6) (2012) 813–820.

[38] T. Matsushita, T. Tateishi, N. Isobe, T. Yonekawa, R. Yamasaki, D. Matsuse, H. Murai, J. Kira, Characteristic cerebrospinal fluid cytokine/chemokine profiles in neuromyelitis optica, relapsing remitting or primary progressive multiple sclerosis, PLoS One 8 (4) (2013) e61835, , https://doi.org/10.1371/journal.pone.0061835.

[39] Michael BD, Elsone L, Griffiths MJ, Faragher B, Borrow R, Solomon T, Jacob A(2013)Post-acute serum eosinophil and neutrophil-associated cytokine/chemokine profile can distinguish between patients with neuromyelitis optica and multiple sclerosis; and identifies potential pathophysiological mechanisms - A pilot study.CYTOKINE 64 (1):90–96. 'doi:'https://doi.org/10.1016/j.cyto.2013.07.019

[40] Uzawa A, Mori M, Masuda S, Muto M, Kuwabara S (2013) CSF high-mobility group box 1 is associated with intrathecal inflammation and astrocytic damage in neuromyelitis optica. Journal of Neurology, Neurosurgery & Psychiatry 84 (5):517–522. 'doi:'https://doi.org/10.1136/jnnp-2012-304039

[41] H. Wang, K. Wang, C. Wang, F. Xu, X. Zhong, W. Qiu, X. Hu, Cerebrospinal fluid high-mobility group box protein 1 in neuromyelitis optica and multiple sclerosis, NEUROIMMUNOMODULAT 20 (2) (2013) 113–118, https://doi.org/10.1159/000345994.

[42] Wang KC, Lee CL, Chen SY, Chen JC, Yang CW, Chen SJ, Tsai CP(2013)Distinct serum cytokine profiles in neuromyelitis optica and multiple sclerosis.J Interferon Cytokine Res 33 (2):58–64. 'doi:'https://doi.org/10.1089/jir.2012.0040

[43] Xu W, Li R, Dai Y, Wu A, Wang H, Cheng C, Qiu W, Lu Z, Zhong X, Shu Y, Kermode AG, Hu X (2013) IL-22 secreting CD4+ T cells in the patients with neuromyelitis optica and multiple sclerosis. J NEUROIMMUNOL 261 (1–2):87–91. 'doi:'10.1016/j.jneuroim.2013.04.021.

[44] P. Horellou, M. Wang, V. Keo, P. Chrétien, C. Serguera, P. Waters, K. Deiva, Increased interleukin-6 correlates with myelin oligodendrocyte glycoprotein antibodies in pediatric monophasic demyelinating diseases and multiple sclerosis, J. Neuroimmunol. 289 (2015) 1–7, https://doi.org/10.1016/j.jneuroim.2015.10.002.

[45] Ichinose K, Arima K, Ushigusa T, Nishino A, Nakashima Y, Suzuki T, Horai Y, Nakajima H, Kawashiri SY, Iwamoto N, Tamai M, Nakamura H, Origuchi T, Motomura M, Kawakami A (2015) Distinguishing the cerebrospinal fluid cytokine profile in neuropsychiatric systemic lupus erythematosus from other autoimmune neurological diseases. CLIN IMMUNOL 157 (2):114–120. 'doi:'https://doi.org/10.1016/j.clim.2015.01.010

[46] Y.J. Li, F. Zhang, Y. Qi, G.Q. Chang, Y. Fu, L. Su, Y. Shen, N. Sun, A. Borazanci, C. Yang, F.D. Shi, Y. Yan, Association of circulating follicular helper T cells with disease course of NMO spectrum disorders, J. Neuroimmunol. 278 (2015) 239–246, https://doi.org/10.1016/j.jneuroim.2014.11.011.

[47] F. Shimizu, H. Nishihara, Y. Sano, Y. Takeshita, S. Takahashi, T. Maeda, T. Takahashi, M. Abe, M. Koga, T. Kanda, Markedly increased IP-10 production by blood-brain barrier in neuromyelitis optica, PLoS One 10 (3) (2015) e122000, , https://doi.org/10.1371/journal.pone.0122000.

[48] Barros PO, Cassano T, Hygino J, Ferreira TB, Centurião N, Kasahara TM, Andrade RM, Linhares UC, Andrade AFB, Vasconcelos CCF, Alvarenga R, Marignier R, Bento CAM (2016) Prediction of disease severity in neuromyelitis optica by the levels of interleukin (IL)-6 produced during remission phase. CLIN EXP IMMUNOL 183 (3):480–489. 'doi:'https://doi.org/10.1111/cei.12733

[49] X. Fan, Y. Jiang, J. Han, J. Liu, Y. Wei, X. Jiang, T. Jin, Circulating memory T follicular helper cells in patients with neuromyelitis optica/neuromyelitis optica spectrum disorders, Mediat. Inflamm. 2016 (2016), https://doi.org/10.1155/2016/3678152.

[50] Kimura K, Nakamura M, Sato W, Okamoto T, Araki M, Lin Y, Murata M, Takahashi R, Yamamura T (2016) Disrupted balance of T cells under natalizumab treatment in multiple sclerosis. Neurology: Neuroimmunology and Neuro Inflammation 3 (2). 'doi:'https://doi.org/10.1212/NXI.0000000000000210

[51] Y. Wang, Y. Zhou, X. Sun, T. Lu, L. Wei, L. Fang, C. Chen, Q. Huang, X. Hu, Z. Lu, L. Peng, W. Qiu, Cytokine and chemokine profiles in patients with neuromyelitis optica spectrum disorder, NEUROIMMUNOMODULAT 23 (5–6) (2016) 352–358, https://doi.org/10.1159/000464135.

[52] Yang T, Wang S, Zheng Q, Wang L, Li Q, Wei M, Du Z, Fan Y (2016) Increased plasma levels of epithelial neutrophil-activating peptide 78/CXCL5 during the remission of Neuromyelitis optica. BMC NEUROL 16:96. 'doi:'https://doi.org/10.1186/s12883-016-0622-3

[53] Zeng Q, Dong X, Ruan C, Hu B, Luo Y, Luo Z, Xu L, Zhou H, Wang R, Yang H (2016) CD14(+)CD16(++) monocytes are increased in patients with NMO and are selectively suppressed by glucocorticoids therapy. J NEUROIMMUNOL 300:1–8. 'doi:'https://doi.org/10.1016/j.jneuroim.2016.09.011

[54] Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG (1999) The clinical course of neuromyelitis optica (Devic's syndrome). NEUROLOGY 53 (5):1107–1114. 'doi:'https://doi.org/10.1212/wnl.53.5.1107

[55] V.A. Lennon, D.M. Wingerchuk, T.J. Kryzer, S.J. Pittock, C.F. Lucchinetti, K. Fujihara, I. Nakashima, B.G. Weinshenker, A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis, LANCET 364 (9451) (2004) 2106–2112, https://doi.org/10.1016/S0140-6736(04)17551-X.

[56] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG (2006) Revised diagnostic criteria for neuromyelitis optica. NEUROLOGY 66 (10):1485–1489. 'doi:'https://doi.org/10.1212/01.wnl.0000216139.44259.74

[57] Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) The spectrum of neuromyelitis optica. LANCET NEUROL 6 (9):805–815. 'doi:'https://doi.org/10.1016/S1474-4422(07)70216-8

[58] Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG(2015) International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. NEUROLOGY 85 (2):177-189. 'doi:'https://doi.org/10.1212/WNL.0000000000001729.

[59] A. Uzawa, M. Mori, S. Kuwabara, Cytokines and chemokines in neuromyelitis optica: pathogenetic and therapeutic implications, Brain Pathol. 24 (1) (2014) 67–73, https://doi.org/10.1111/bpa.12097.