Original Article

Altered pro-inflammatory and anti-inflammatory plasma cytokines levels in children with Down's syndrome: A meta-analysis

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Abstract

Background: Down syndrome (DS) is the commonest chromosomal anomalies at birth. DS is portrayed by the event of extra complete/deficient duplicate of chromosome number 21 (trisomy 21). Around the world, this disordered influencing roughly 1 out of 1000 infants. Pro-inflammatory and anti-inflammatory cytokines engaged with a few physiological procedures involving the guideline of inflammatory reactions. In DS kids, the creation of few important inflammatory and anti-inflammatory cytokines is altered. Different investigations shows that the cytokines are dysregulated in patients with DS. In this study, we led a meta-analysis to evaluate the connections of pro-inflammatory and anti-inflammatory cytokine changes in youngsters with DS patients. **Methodology:** We searched PubMed, Google and Web of Science for studies in exploring the association of pro-inflammatory and anti-inflammatory serum level with DS patients. Total 10 studies were included in the meta-analysis. The random effects were used to analyze the pooled data. All statistical tests were two-sided. **Results:** High circulating level of serum MCP-1 was significantly associated with DS [Cohen's d = 143.91 95% confidence interval (CI) =110.38-177.43]. However, the other circulating cytokines IL-2 and IL-17 level were lower whereas IL-13 level was higher but not significantly different in DS as contrasted to healthy controls. The heterogeneity level was higher in IL-2, IL-13 and IL-17 cytokines. **Conclusion:** This meta-analysis shows that the higher circulating level of MCP-1 was associated with DS.

Keywords: Cytokines, down syndrome, genetic disorder, inflammation, meta-analysis

Introduction

Down Syndrome (DS) or trisomy 21 is a hereditary disorder which is described by phenotype such as magnolian like face diminished developmental growth. The maternal age and reduce folate-homocysteine metabolism are major risk factors for DS.[1,2]

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Received: 19-02-2021 **Revised:** 25-03-2021
Accepted: 04-04-2021 **Published:** 05-11-2021

Access this article online
Quick Response Code:
Website: www.jfmpc.com
DOI: 10.4103/jfmpc.jfmpc_364_21

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How to cite this article: Nigam N, Singh PK, Raizada N, Singh BP, Tripathi S, Agrawal M, *et al*. Altered pro-inflammatory and anti-inflammatory plasma cytokines levels in children with Down's syndrome: A meta-analysis. J Family Med Prim Care 2021;10:3568-74.

Around the world, roughly in excess of 5 million people are influenced by DS and in the United States, the predominance of DS in between 2.5-4 lakh.[3] Total 94,910 babies of three Indian metropolitan urban areas (Baroda, Mumbai and Delhi) study, the DS recurrence was observed 1 for every 1150.[4] This genetic disorder is the most common cause of neonatal mortality in cities.[5] Moreover, mental disabilities and neuropathological changes are quite common in DS, which subsequently leads to Alzheimer's disease, whereas minimum 70% of patients will develop dementia between 55–60 years of their age.[6-9] Till date, there are no current medicines to forestall and build the span of the advancement of dementia in grown-up DS patients. The altered immune response is significantly associated with DS and which make more susceptibility to bacterial or viral infection.[10] A previous study described that the amyloid-beta plagues had accumulated in DS patients brains which may lead to the development of dementia.[6] The extra potential pathogenic relationship among DS and Alzheimer's-ailment is the modification of resistant reaction in the focal and fringe nervous system of the patients. This is demonstrated by active glial cell with greater inflammatory markers expression like chromosome-21 and chromosome-2 gene, which produce S100B and IL-1 in DS and Alzheimer's-disease brains, respectively.[11,12]

The pro-inflammatory cytokines, for example, IL-1β, IL-2, IL-6 and IL-17, assume significant jobs in provocative reactions. The T-cells and macrophages produce IL-6 which activates the inflammatory responses, whereas IL-1β enhances the maturation of B cell maturation and persuades the production of immunoglobulin, which ultimately causes inflammation.[13] To better understanding of the etiology of the diseases these inflammatory cytokines and chemokines can be used as potential biomarkers in disease progression while all the clinical or scientific facts were not always steady throughout worldwide.

A previous meta-examination shows that the degree of inflammatory cytokines, for example, neopterin, IL-1β, TNF-α and IFN-γ were essentially expanded in DS youngsters when contrasted with healthy kids.[14] Moreover, the alteration in inflammatory and anti-inflammatory cytokines level in DS affected individuals was quite imprecise because of the inconsistent data related to cytokine.[15-17]

The helper T (Th0) cells get differentiated into the Th2 cells by IL-4 cytokine, which assumes a key role in the regulation of humoral and adaptive immunity.[18] IL-10 is mostly produced by monocytes whereas lymphocytes produce smaller amount. This cytokine has multiple effects on inflammation and immunoregulation. It also increases the proliferation of B cell and antibody production. It is capable of forestalling the creation of pro-inflammatory cytokines, for instance, IL-2, IL-3, IL-6 and IL-17.[19] Cytokine IL-13 produce by different cells such as Th-2 cells. It plays a vital role in physiological changes influenced by allergic inflammation in various tissues.[20]

Chemokine, for example, monocyte chemoattractant protein-1 (MCP-1) assumes a fundamental job in the inflammation.[21] Past examination recommended that the degree of MCP-1 in Alzheimer ailment may assume a fundamental role in the observing of inflammation procedure.[22] The up-regulatory properties of IL-6 and MCP-1 have been shown in Alzheimer's neurodegenerative disease.[23] The children with DS have a high level of IL-6 and MCP-1 cytokines. There is evidence demonstrating that after the 50 years of age, the individuals suffering from DS have a greater risk of development of Alzheimer's disease.[24]

Till date, there was no study led on pro-inflammatory and anti-inflammatory cytokines levels in youngsters with DS in north Indian Population. In this way, we plan to assess the pro-inflammatory and anti-inflammatory cytokines levels in DS patients. The meta-examination on this subject is basic to shows the inconsistency in clinical or logical information, especially in the difference in the level of pro-inflammatory and anti-inflammatory cytokine in DS kids. In this study, we aim to clarify the evidence base available around the relationships of pro-inflammatory and anti-inflammatory cytokine changes in children with DS. Clarification will be made by a meta-analysis of the evidence-based journals and abstracts in this topic area, looking at all designs of study.

Materials and Methods

Setting and study design

This meta-analysis study will be done in department of Center for Advance Research (CFAR), Cytogenetics Lab, King George's Medical University Lucknow.

Search and selection methods of studies

We looked PubMed, Google, ResearchGate and Web of Science for contemplates evaluating the cytokines level in serum and Down syndrome or trisomy 21 patients from 2001 to February 2020. The research term was Down syndrome or Trisomy 21 or DS or Down Syndrome Anomalies or Trisomy 21 Anomalies or DS Anomalies or Chromosomal Disorder or Genetic Disorder or Congenital Disorder or Neonatal anomalies, Child anomalies or Cytokines or Inflammatory Cytokines or Pro-inflammatory Cytokines or Anti-Inflammatory Cytokines, Chemokines, Interleukins or IL, Monocyte Chemoattractant Protein-1, MCP-1, Enzyme-Linked Immunosorbent Assay or ELISA. Results were restricted to serum IL-2, IL-13, IL-17 and MCP-1 detection in human Down syndrome or trisomy 21. A total of 923 entries were recognized in PubMed, Google and Web of Science.

The cytokines measurement by Enzyme-Linked Immunosorbent Assay (ELISA) and other assay, accessible information of DS and controls and publication in English were included in this study. Original clinical or scientific studies data on circulating pro and anti-inflammatory cytokine level in Down syndrome patients and controls were included.

The studies show the gene expression of cytokines, identifying cytokines level in tissues, animals or in lab were excluded from the study. The relationship of cytokines with DS and control was the key concern for the selection of the study. Cytokines was be not analyzed in at least two studies. Cut-offs levels of cytokines were characterized by unique studies classified DS patients into higher and lower groups.

Information collection

Information was individually extricated by each author as per inclusion criteria. The various details such as types of cytokines (IL–2, IL-13, IL-17 and MCP-1), technique for cytokines detection, number of patients and controls, gender, mean age and sample source were collected from each study [Table 1].

Data synthesis

The information was recorded from each examination, for example, Title of the article, name of the principal author's, name of the journal, publication year, name of nation and technique utilized for test type.

Statistical analysis

We utilized RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) meta-analysis programming to accomplish all the statistical estimations. In present study, all the study data were collected from different article and combined in this meta-analysis primarily. The statistical heterogeneity was assessing Cochran's Q and I^2 statistics. The sample sizes of the study, mean ± SD (standard deviation) concentration of pro-inflammatory and anti-inflammatory cytokines were mostly used to make effective size. The actual effective size was measured as a mean concentrations difference of the pro-inflammatory and anti-inflammatory cytokine in DS cases and controls, and changed to Hedges'g which gives a fair balanced effective size. All measurable investigation was both sided. The P value < 0.05 are considered significant.

Results

Search results

The search outcomes of articles have been shown in Figure 1. Initially, total 923 research articles were recorded. After title of references, we were rejected 874 records on account of the insignificance with the examination point and copied articles. Subsequent, 30 title citations were also excluded from the study after screening abstracts of the articles. Finally, after the scanning of titles and abstracts of the articles, we select the 19 articles for full text analysis. Numerous literatures were excluded from the study because: no necessary data (3), animal studies (2) and cytokines will be not examined in a minimum two studies (4). Thus, an aggregate of 10 studies were incorporated for the meta-analysis which encompasses 485 DS patients and 381 healthy controls.[15,16,25-32]

Random effects meta-analysis shows DS patients had lower but not statistically different in the circulating levels of cytokines marker as compared to healthy controls for IL-2 (Cohen's d=-4.55, 95% CI = -9.23 to 0.13, $P = 0.06$) and IL-17 (Cohen's d=-20.26, 95% CI = -62.70 to 22.17, $P = 0.35$) whereas IL-13 level had higher but not significantly different circulating as compared with healthy controls (Cohen's d = 11.57, 95% CI = -17.95 to 41.09, $P = 0.44$). The circulating MCP-1 level had statistically significant higher in DS as compared to healthy controls (Cohen's d = 143.91 95% CI = 110.38 to 177.43) as shown in Table 2.

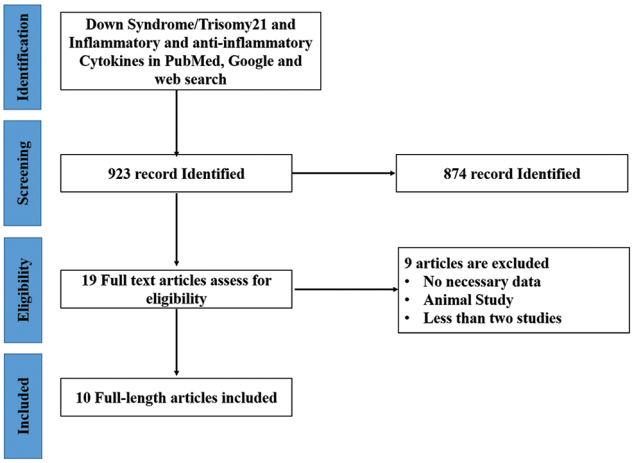

Figure 1: Selection of studies included in the analysis of Cytokines (IL-2, IL-13, IL-17 and MCP-1)

Table 1: Characteristics of included studies for circulating cytokine concentration analysis

Studies	Country	Types of Cytokines Measured	Number of DS patients/Control	Sample Source	Assay type
Cetiner *et al.* 2010[15]	Turkey	IL-2	32/32	Blood	ELISA
Huggard *et al.*, 2020[27]	Ireland	IL-2	114/60	Blood	Multiplex ELISA
Śmigielska-Kuzia *et al.*, 2012[25]	Bialystok	IL-2	84/39	Blood	ELISA
Abdel-Salam *et al.*, 2013[28]	Egypt	IL-2	60/30	Blood	ELISA
Akhmatova and Akhmatova, 2017[26]	Russian	IL-2, IL-17	49/56	Blood	ELISA
Dogliotti *et al.*, 2010[32]	Italy	MCP-1	23/30	Blood	Biochip array analyzer
Corsi *et al.*, 2006[31]	Italy	MCP-1	23/20	Blood	Immunoenzymatic kit
Smigielska-Kuzia *et al.*, 2010[29]	Poland	IL-13	20 (3)/5 (33)	Blood	ELISA
Nateghi Rostami *et al.*, 2012[16]	Iran	IL-13	24/24	Blood	ELISA
Tsilingaridis *et al.*, 2012[30]	Sweden	IL-17	24/29	Blood	Flow Cytomix Thl/Th2 10 plex kit

DS: Down syndrome; IL: interleukin; MCP: Monocyte chemoattractant protein; ELISA: enzyme linked immunosorbent assay; HPLC, NA: not available

Table 2: Comparative outcomes for circulating cytokine measurements

Cytokine	No. of studies	No. with DS/Controls	Main effects			Heterogeneity				
			Cohen's d (95% CI)	*Z* score	*P*	Tau^2	Chi^2	df	*P*	I^2 Statistic
IL-2	4	339/217	-4.55 (-9.23-1.13)	1.91	0.06	28.37	2418.18	4	<0.001*	100%
IL-13	2	27/29	11.57 (-17.95-41.09)	0.77	0.44	378.29	5.02	1	0.03*	80%
IL-17	2	73/85	-20.26 (-62.70-22.17)	0.94	0.35	936.36	863.42	1	<0.001*	100%
MCP-1	2	46/50	143.91 (110.38-177.43)	8.41	<0.001	210.04	1.56	1	0.21	36%

*Significant (P<0.05)

In this meta-analysis the heterogeneity was significantly found in IL-2, IL-13 and IL-17 cytokines. Moreover, the cytokines IL-2 and IL-17 are showed high levels and IL-13 is showed the moderate heterogeneity levels [Table 2].

Subgroup analysis

Then we accomplished subgroup examination in between study. Meanwhile maximum studies analyzed the levels of cytokine in DS children (age <12 years), so, we performed this meta-analysis to examine the pro-inflammatory and anti-inflammatory cytokine alteration in DS children. As shown in Figure 2, DS children had significantly increased level of MCP-1 (2 studies, Cohen's d = 143.91 95% confidence interval (CI) =110.38 to 177.43), $P < 0.001$) when contrasted with healthy control. Moreover, DS patients had increased levels of IL-13 (2 studies, Cohen's d = 11.57, 95% CI = -17.95 to 41.09, $P = 0.44$) when compared to healthy control children, whereas it did not statistically different. Whereas children with DS had lower IL-2 (5 studies, Cohen's d= -4.55, 95% CI = -9.23 to 0.13, $P = 0.06$) and IL-17 (2 studies, Cohen's d=-20.26, 95% CI = -62.70 to 22.17, $P = 0.35$) levels as compared to healthy control children, whereas it did not statistical significant different. However, the heterogeneity remains high between study for IL-2 ($Tau^2 = 28.37$; $P < 0.001$; $I^2 = 100\%$), IL-13 ($Tau^2 = 378.29$; $P = 0.03$; $I^2 = 80\%$) and IL-17 ($Tau^2 = 936.36$; $P < 0.001$; $I^2 = 100\%$).

Sensitivity analyses

Sensitivity analyses suggested that no single examination was altogether biased the distinction on circulating level of pro-inflammatory and anti-inflammatory cytokines (IL-2, IL-13, IL-17 and MCP-1) among DS patients and healthy controls.

Discussion

In this meta-analysis to explore the changes of circulating pro-inflammatory and anti-inflammatory cytokines level in DS kids compared with controls. In this, we analyzed the available data the level of cytokines in 485 DS patients from 10 published articles and particularly the changes of cytokine in patients as compared with controls (n = 381).

The abnormal production of various cytokines has been correlated with the pathophysiology of DS.[33,34] Moreover, the increased level of peripheral circulation inflammatory cytokines may perform a key role in mental retardation, augmented the exposure to the phenomena of infections and autoimmune in DS.[33-35] These abnormalities in circulation blood cytokines might reason of neuronal cell death, through apoptosis by T-lymphocytes dysfunction in DS, but the facts remain unidentified.[36,37] Overexpression of IL-1, play out a fundamental role in the turn of events and movement of neuronal degeneration in DS patients.[34]

Previously published studies demonstrated that the abnormal levels of inflammatory cytokines and active central nervous system microglial cells perform a significant role in the development and progression of Alzheimer's and Parkinson' disease related to neurological disorders.[38-41] Previous meta-analyses have been demonstrated that the concentrations of inflammatory cytokine TNF-α, TGF-β, IL-1β, IL-6, IL-12 and IL-18 were higher in Alzheimer's disease (AD) and TNF-α, IL-1β, IL-2, IL-6, IL-10 were more elevated in Parkinson' disease.[9,42]

Another meta-analyses study has been examined the circulating level of inflammatory cytokine in DS patients. This meta-examination revealed that the more significant level of circling IFN-γ, IL-1β, neopterin and TNF-α were available in DS patients.[14] The findings support the clinical indication suggested that an irregular inflammatory response escorts the DS children. Similarly, in this meta-analysis, the levels of neopterin and TNF-α were expanded in DS patients. Whereas the circulating INF-γ level was near to significant ($P = 0.08$) in DS patients. Previous studies reported that the MCP-1 was elevated in DS patients. Its shows an important role in the inflammation and regulate the neurodegenerative disease.[21-24]

In this random effect meta-investigation, we found that the MCP-1 had significantly higher circulating levels in patients with DS when contrasted with controls (Cohen's d = 143.91 95% CI = 110.38-177.43). Corsi *et al.* (2006)[31] and Dogliotti *et al.* (2010)[32] reported that plasma levels MCP-1 were raised in DS patients when contrasted with control. This higher level of MCP-1 could not be recognized to scientific inflammation; meanwhile there was no measurable pathological situation in DS patients. In this way, it is conceivable that the degree of MCP-1 was high in DS patients because of initiation of endothelial without immune responses activation. Down syndrome/trisomy 21 is the commonest chromosome anomaly among neonates. These infants commonly develop a transient myeloproliferative disorder (TMD). In which few infants suffer from life-threatening complications, like liver fibrosis.[43-45] Previous study reported that hepatic stellate cells (hSCs) performed an essential role in liver fibrosis.[46] In this way the pro-fibrogenic chemokines like

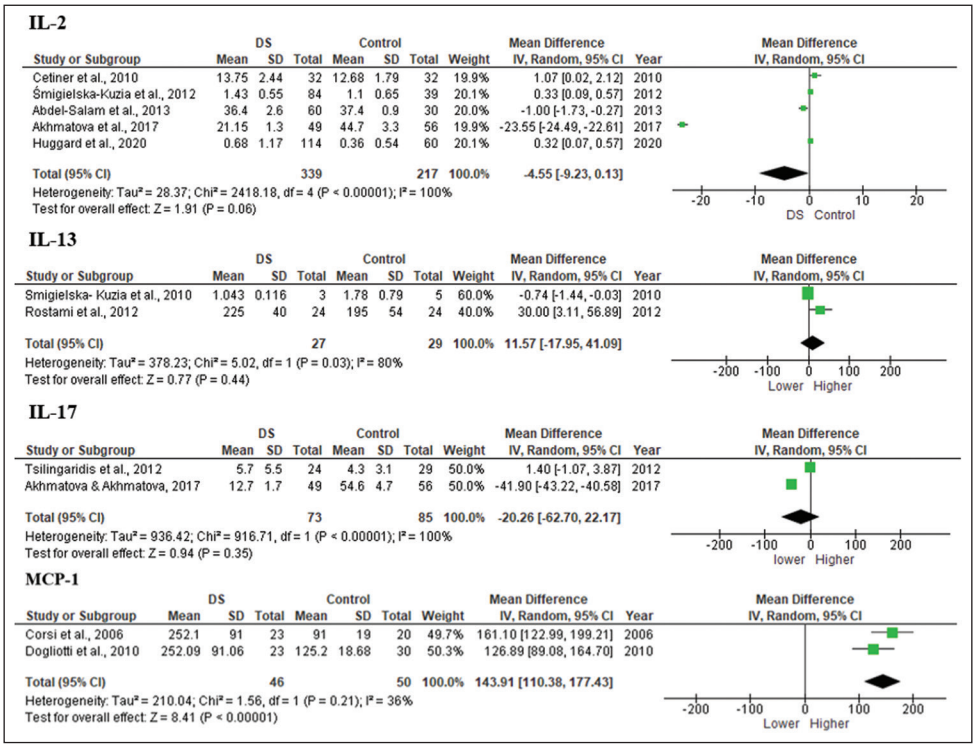

Figure 2: Forest plot showing the random effects meta-analysis outcome in association between IL-2, IL-13, IL-17 and MCP-1

hSC-derived CC and CXC have been recognized as an objective theme against cytokine treatment for liver diseases.[47,48]

In which MCP-1 is one of the best biomarkers for posttraumatic liver failure or liver cirrhosis.[46,49,50] Thus, the serum level of MCP-1 was higher in DS patients may cause liver fibrosis. Various previous studies also suggested that the MCP-1 has been showed up-regulatory properties in neurodegenerative disease.[21,22] In this way, these proofs proposed that the DS have an incredible hazard for building up Alzheimer's illness in more established age.[24]

Our results showed that the circulating cytokines IL-2 and IL-17 level were not statistically lower in patients with DS as compared to controls. Whereas IL-13 level had higher but not significantly different circulating as compared with healthy controls. The heterogeneity was significantly found in IL-2, IL-13 and IL-17 cytokines examined in this meta-analysis. The cytokines IL-2, IL-13 and IL-17 showed high levels of heterogeneity. Our results are supported by similar findings of previous study; they reported that the circulating level of cytokine IL-2 was not statistically different in between DS patients and healthy controls. IL-2 cytokine was not statistically different in between DS patients and controls (36.4 ± 2.6 vs. 37.4 ± 0.9).[28] On the contrary to our meta-analysis, various studies reported that the concentration (pg/ml) of IL-2 level was significantly different in between patients with DS and healthy controls.[17,24,27,30,32,33] They reported that the concentration (pg/ml) of IL-2 was statistically higher in patients with DS when contrasted with controls.

Our finding of IL-13 cytokine may likewise start the creation of immunoglobulin E (IgE) by human B cells perceived that an extra layer of trouble introduced in the guideline of IgE.[29]

Our country has a limited number of geneticists, immunologists and neurologists. And almost all of them are concentrated in Metro and big cities. Remote rural areas and difficult terrains lack presence of experts where primary care physicians assess and provide essential care. As patients of chromosomal anomalies, including Down's Syndrome, are present everywhere, it's necessary to equip their career with basic knowledge regarding detection of early signs of neurodegenerative and inflammatory diseases in this patient population.

Based on this knowledge base, if primary care providers timely detect and refer such patients early on in their natural course of the complicated illness, it's known that the disability can be managed well. Conversely when primary care providers delay in detecting such early signs, and consequently specialists get patients late in their natural history, only limited rehabilitation is possible. Therefore, we decided to send this meta-analysis to a journal targeting those providing primary care to masses for wider dissemination of results of our study.

Conclusion

This meta-analysis shows that the higher circulating level of MCP-1 was associated with DS patients. However, the other circulating cytokines IL-2 and IL-17 level were lower whereas IL-13 level was higher but not significantly different in patients

with DS when contrasted with healthy controls. The cytokines IL-2, IL-13 and IL-17 showed high levels of heterogeneity. The findings support the clinical evidence for abnormal inflammatory response of the cytokines in DS patients.

Key point

- The higher circulating level of MCP-1 was associated with DS patients.

Highlight

- The MCP-1 had significantly higher circulating levels in patients with DS when contrasted with controls.
- This higher level of MCP-1 could not be recognized to scientific inflammation; meanwhile there was no measurable pathological situation in DS patients.
- The circulating cytokines IL-2 and IL-17 level were not statistically lower in patients with DS as compared to controls.
- The circulating IL-13 level had higher but not significantly different as compared with healthy controls.
- The heterogeneity was significantly found in IL-2, IL-13 and IL-17 cytokines.

Financial support and sponsorship

This work was financially supported by an intramural grant from King George's Medical University, Lucknow [No. 487/R.cell-19].

Conflicts of interest

There are no conflicts of interest.

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