Clinical and Experimental Health Sciences

Increased Systemic Inflammatory Response with Mast Cell Activation In Elder Children With Cerebral Palsy

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ABSTRACT

Objective: Increased systemic inflammatory response during intrauterine period or period before the age of 3 is associated with cerebral palsy (CP) pathogenesis; however, effects of inflammatory processes involving mast cell activation in elder children with CP remain unclear. We aimed to investigate the role of mast cells and proinflammatory cytokines in children with CP at 3-18 years of age.

Methods: In this cross-sectional study, venous blood samples were obtained from 30 volunteers with CP and 26 healthy volunteers at 3-18 years of age. Plasma levels of proinflammatory cytokines (IL-1β, IL-6 and IL-9) and mast cell biomarkers (histamine and tryptase beta-2) were determined using ELISA.

Results: IL-1β, IL-6 and histamine levels were higher in individuals with CP compared to healthy controls. Likewise, IL-1β, IL-6, IL-9 and histamine levels were higher in the female patients with CP compared to the male patients, and in the female patients in adolescence compared to the female patients in pre-adolescence.

Conclusion: Our findings indicate that the increased inflammatory response contributes to the pathogenesis of the disease in children with CP who are older than 2 years of age. Moreover the increased inflammatory response is more effective in female patients than in male patients, suggesting that there may be a gender difference in CP. Additionally mast cell activation contributes to the exacerbation of systemic inflammatory response in children with CP at 3-18 years of age.

Keywords: Cerebral palsy, Children, Inflammation, Mast cells, Cytokines, Gender.

1. INTRODUCTION

Cerebral palsy (CP) is one of the main disabling disorders, characterized by permanent brain damage that affects motor and cognitive functions with different clinical symptoms in children (1). Cerebral palsy has a complex etiology that involves intrauterine pathologies, intrapartum complications, and postpartum sequelae.

Central nervous system injury is multifactorial and involves the exposure of the fetus or the newborn to acute and chronic inflammation, or perinatal hypoxia-ischemia (2). Neuronal lesions related to inflammation lead to the initiation of a series of immune responses, including an increase in circulating cytokines, particularly interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor alpha (TNF-α), which may be involved in the development of brain injury (3).

In the previous studies, it was demonstrated that there was a relationship between high levels of proinflammatory cytokines such as TNF-α, IL-6 and IL-8 in the amniotic fluid, plasma or umbilical cord blood and, the occurrence of cerebral palsy and periventricular leukomlacia, the common white matter damage of the brain (4-6). In the meantime, the clinical evidence indicating higher plasma IL-1, IL-8, IL-9 and TNF-α levels in children with cerebral palsy compared to the healthy controls also supports the role of proinflammatory cytokines in the pathophysiology of CP (3,7,8). Thus, the relationship between the inflammation triggered by proinflammatory cytokines in various developmental processes, mentioned above, and the CP pathogenesis has been well established. Yet, clinical studies revealing this relationship have focused on the postnatal period of children with cerebral palsy from the prenatal period to 3 years of age. On the other hand, the

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relationship between proinflammatory cytokines and the course of the disease is unknown in children with CP after 2 years of age. Moreover, it is not clear whether inflammation in the pathogenesis of CP varies by gender and developmental periods. Therefore, clarification of the pathophysiological processes and possible gender and developmental period differences in the course of the disease in childhood after the age of 2 is of vital importance.

Mast cells are the multifunctional immune cells that are one of the most important sources of proinflammatory cytokines. The preclinical studies reporting that the deficiency of mast cells or the stabilization of mast cells by cromolyn substantially reduced brain lesions in different experimental models (9,10) indicated that the mast cells may play an important role in inflammatory processes associated with the pathogenesis of CP. Nevertheless, studies investigating the role of mast cell activation in the pathogenesis of CP are limited to experimental animal studies; and clinical studies are needed on this subject.

In the present study, we aimed to compare the concentrations of plasma proinflammatory cytokines and, the markers of mast cell count and activation in children diagnosed with CP older than 2 years of age, with the healthy individuals of the same age, thereby investigating the relationship between proinflammatory cytokine levels and mast cell activation in elder children with CP. In addition, we aimed to investigate if there is a difference in terms of these cytokines and mast cell markers, whether this difference changes according to the gender and developmental periods.

2. METHODS

2.1. Subjects

The research protocol was approved by the Bolu Abant Izzet Baysal University Clinical Research Local Ethics Committee (approval number 2018/181). This cross-sectional study included children with clinically confirmed CP, who were diagnosed with CP at the Pediatric Neurology department in one of the hospitals in Western Black Sea region between November 2018 and June 2019 and were benefiting from the rehabilitation services at the *Izle Special Education and Rehabilitation Center* located in Duzce city. The study was participated by 30 volunteering individuals with CP between 3-18 years of age (15 male, 15 female), and 26 volunteering healthy individuals of the same age group in the control group (14 male, 12 female). Inclusion criteria for the group of patients with CP were, i) being clinically diagnosed with CP, ii) being between the ages of 3-18, iii) having stable health conditions; and the exclusion criteria were, i) having any chronic (neuro)inflammatory diseases (autoimmune or microbial), ii) having any type of infection, iii) having any type of chronic mast cell disease (mastocytosis etc. Healthy controls were term born and normal born individuals with no diseases. All of the healthy controls and the patients were from the the Western Black Sea Region of Turkey. The demographic and clinical characteristics of the patients and healthy controls are presented in Table 1 and Table 2.

2.2. Study design

In accordance with the Helsinki Declaration, signed and informed consent was obtained from all volunteering healthy controls, patients and their parents. Age, gender, type of CP, height, weight, body mass index and ambulation characteristics were recorded for the patients. Age, gender, height, weight, body mass index and findings of the normal physical and neurological examinations were recorded for the healthy individuals in the control group. From each volunteering patient and individual in the control group, a blood sample of 5 ml was taken from the median cubital vein for once, while resting in a sitting position between 09:00 and 12:00 in the morning. Blood samples were immediately transferred to ice-cold glass tubes containing anticoagulant EDTA. The blood was then centrifuged at 3000 rpm, 4°C for a period of 15 minutes. Supernatants were stored at – 80°C until their immunoreactivity was determined against proinflammatory cytokines IL-1β, IL-6 and IL-9 as well as the mast cell count and activation markers histamine and tryptase beta-2, using the ELISA method.

2.3. Measurement of plasma IL-1β, IL-6, IL-9, histamine and tryptase beta-2 concentrations

IL-1β, IL-6, IL-9, histamine and tryptase beta-2 contents in the samples were measured by enzyme-linked immunosorbent assay kits (BT Lab, Shanghai, China). The detection limit was 10.07 pg/L for IL-1β, 1.03 ng/L for IL-6, 9.83 pg/mL for IL-9, 0.51 ng/mL for histamine, and 36.15 ng/L for tryptase beta-2, respectively. Assay protocols were performed in duplicate according to the instructions of the manufacturer. In brief, 50 µL of IL-1β, IL-6, IL-9, histamine and tryptase beta-2 standard was added to the standard wells. Then, 40 µL of plasma samples, and 10 µL of antibodies of these markers were added to the sample wells. Then, 50 µL streptavidin-HRP was added to each well. Then, the 96-well plates were incubated at 37 °C for 60 min. After washing the 96-well plates 5 times with wash buffer, 50 µL substrate solution A and B were added to each well, and the plates were incubated at 37 °C for 10 min. After the incubation, 50 µL stop solution was added to each well. The optical density of the wells was measured at 450 nm using a microplate reader (Epoch BioTek Instruments, Inc. Highland Park, Winooski, VT, USA). Optical density curves were obtained using the standards with defined IL-1β, IL-6, IL-9, histamine and tryptase beta-2 concentrations.

2.4. Statistical analysis

Data were given as median values, and first and third quartiles. SPSS statistical package program was used for the statistical analysis of the data obtained from the study (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, NY, USA). The data distribution was analyzed for normality using the Shapiro-Wilk-W test. For the comparison of the two independent groups, independent sample t-test or Mann-Whitney U test was used. The level of $p<0.05$ was considered statistically significant.

Table 1. *Demographic and clinical characteristics of subjects with cerebral palsy for each patient.*

Patient	Gender	Classification	Age	Height (cm)	Weight (kg)	BMI (kg/m2)	Ambulation
1	Male	Spastic – Hemiplegic	10	135	40	21,9	Yes
2	Female	Spastic – Kuadriplegic	4	90	12	14,8	No
3	Male	Spastic – Diplegic	15	160	52	20,3	Yes
4	Female	Spastic – Hemiplegic	4	110	20	16,5	Yes
5	Male	Spastic – Hemiplegic	9	125	30	19,2	Yes
6	Female	Spastic – Hemiplegic	11	148	36	16,4	Yes
7	Male	Spastic – Diplegic	9	150	45	20	Yes
8	Female	Spastic – Hemiplegic	4	112	18	14,3	Yes with orthosis
9	Male	Spastic – Hemiplegic	4	108	19	16,2	Yes
10	Male	Spastic – Diplegic	16	165	70	25,7	Yes
11	Female	Ataxic	14	155	55	22,8	Yes
12	Male	Ataxic	11	156	42	17,2	Yes
13	Female	Spastic – Kuadriplegic	8	117	18	13,1	No
14	Female	Spastic – Diplegic	5	102	15	14,4	Yes with orthosis and walker
15	Male	Spastic – Hemiplegic	10	140	28	14,2	Yes
16	Female	Spastic – Diplegic	11	152	53	22,9	Yes with orthosis and walker
17	Male	Spastic – Hemiplegic	3	90	18	22,2	Yes
18	Female	Spastic – Kuadriplegic	17	153	65	27,7	No
19	Female	Spastic – Diplegic	5	98	14	14,5	Yes with orthosis and walker
20	Male	Spastic – Diplegic	15	158	60	24	Yes with orthosis and walker
21	Male	Spastic – Hemiplegic	8	132	23	13,2	Yes
22	Male	Spastic – Diplegic	10	133	30	16,9	No
23	Female	Spastic – Hemiplegic	8	112	19	15,1	Yes
24	Male	Spastic – Diplegic	6	98	16	16,6	Yes with orthosis and walker
25	Female	Spastic – Diplegic	13	165	60	22	Yes with orthosis and walker
26	Female	Spastic – Hemiplegic	11	135	43	23,5	Yes
27	Female	Spastic – Kuadriplegic	15	145	56	26,6	No
28	Male	Spastic – Hemiplegic	8	122	30	20,1	Yes
29	Female	Spastic – Diplegic	14	150	65	28,8	Yes with orthosis and walker
30	Male	Spastic – Diplegic	16	168	49	17,3	Yes with orthosis and walker

Table 2. *Demographic and clinical characteristics of healthy control subjects.*

Subject	Gender	Age	Height (cm)	Weight (kg)	BMI (kg/m2)	Physical examination	Neurological examination
1	Female	16	155	58	24,1	Normal	Normal
2	Male	15	175	88	28,7	Normal	Normal
3	Male	14	170	75	25,9	Normal	Normal
4	Male	10	133	43	24,3	Normal	Normal
5	Female	8	130	32	18,9	Normal	Normal
6	Male	14	158	57	22,8	Normal	Normal
7	Female	11	140	45	22,9	Normal	Normal
8	Male	11	149	44	19,8	Normal	Normal
9	Female	9	125	28	17,9	Normal	Normal
10	Female	12	155	48	19,9	Normal	Normal
11	Female	5	102	16	15,3	Normal	Normal
12	Female	9	139	33	17	Normal	Normal
13	Female	7	118	20	14,3	Normal	Normal
14	Female	7	125	23	14,7	Normal	Normal
15	Female	6	120	20	13,8	Normal	Normal
16	Male	9	140	35	17,8	Normal	Normal
17	Male	17	169	70	24,5	Normal	Normal
18	Male	15	165	55	20,2	Normal	Normal
19	Male	12	160	49	19,1	Normal	Normal
20	Male	14	167	55	19,7	Normal	Normal
21	Female	9	135	35	19,2	Normal	Normal
22	Male	14	152	60	25,9	Normal	Normal
23	Male	13	173	57	19	Normal	Normal
24	Male	3	102	21	20,1	Normal	Normal
25	Male	9	125	27	17,2	Normal	Normal
26	Female	11	140	35	17,8	Normal	Normal

3. RESULTS

Venous blood samples were obtained from 30 volunteers (15 male) with CP (mean age, 9.8±4.2 years) and 26 healthy controls (14 male) (mean age, 10.7±3.5) between the ages of 3-18. The mean age of individuals with CP was not statistically different compared to the healthy individuals in the control group (P=0.362, independent sample t-test). Body mass index value (BMI) of individuals with CP (19.2±4.5) was not statistically different from compared to the healthy controls (20.0±3.8) (P=0.513, independent sample t-test).

3.1. High plasma proinflammatory cytokine levels and mast cell activation in patients with cerebral palsy

Since plasma IL-1β, IL-6, IL-9, histamine and tryptase beta-2 values were not normally distributed in the control and CP groups, they were compared using the Mann-Whitney U test. The plasma levels of proinflammatory cytokines IL-1β (P=0.021, Fig 1A) and IL-6 (P=0.037, Fig 1B) and also the plasma level of histamine (P=0.002, Fig 1D), which indicates mast cell activation, were significantly higher in the CP group compared to the healthy controls. On the other hand, there was no significant difference between patients with CP and the healthy controls in terms of the plasma levels of proinflammatory cytokines IL-9 (P=0.411, Fig 1C) and tryptase beta-2 (P=0.593, Fig 1E), which is a marker of increased count of mast cells.

3.2. High plasma IL-1β, IL-6, IL-9 and histamine levels in female patients with cerebral palsy, but not in male patients, compared to healthy female controls

Since plasma IL-1β, IL-6, IL-9, histamine and tryptase beta-2 values were not normally distributed in the control and CP groups, the independent paired groups were compared using the Mann-Whitney U test. In the female gender, the plasma levels of IL-1β (P=0.006, Fig 2A), IL-6 (P=0.005, Fig 2B), IL-9 (P=0.003, Fig 2C), and histamine (P=0.017, Fig 2D) were found to be significantly higher in the CP group (n=15) compared to control group (n=12). Nonetheless, there was no significant difference in terms of tryptase beta-2 (P=0.205, Fig 2E). On the other hand, in the male gender, none of these values differed between control (n=14) and CP (n=15) groups (P>0.05 for all unpaired comparisons, Fig 2A-E).

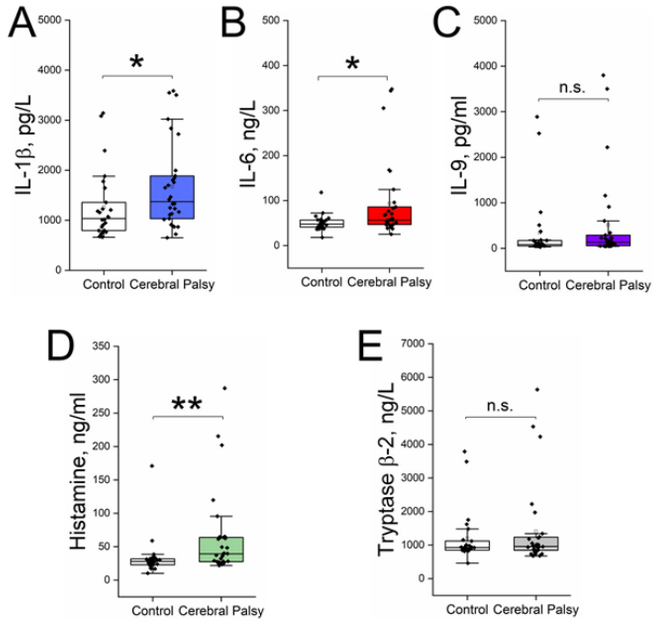

Figure 1. *High plasma IL-1β, IL-6 and histamine levels in subjects with cerebral palsy compared to healthy controls. Each box represents the median±SD, minimum and maximum values of the results. Plasma levels of these mediators between the cerebral palsy and control groups are compared by Mann-Whitney U test. n.s.: non-significance, *P < 0.05 and ** P < 0.01.*

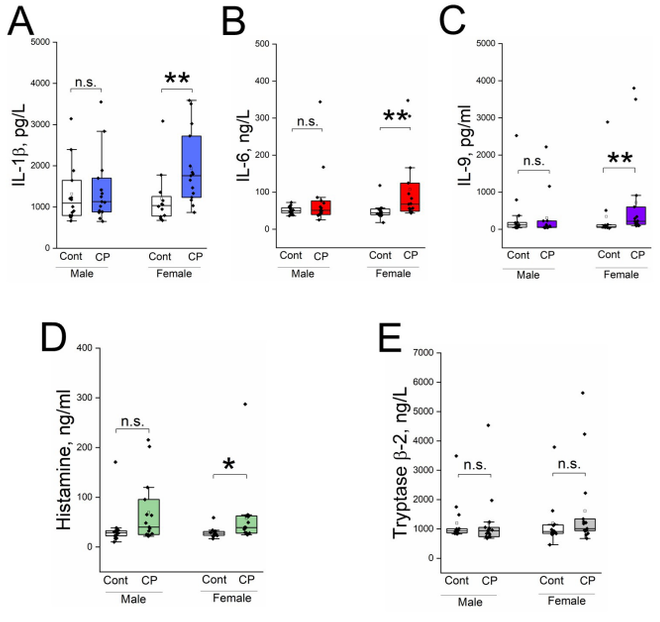

Figure 2. *High plasma IL-1β, IL-6, IL-9 and histamine levels in female subjects with cerebral palsy compared to healthy female controls. Each box represents the median±SD, minimum and maximum values of the results. Plasma levels of these mediators between the cerebral palsy and control groups are compared by Mann-Whitney U test. n.s.: non-significance, *P < 0.05 and ** P < 0.01.*

3.3. High plasma IL-1β and IL-9 levels in the females compared to the males in the group of patients with cerebral palsy.

Since plasma IL-1β, IL-6 and IL-9 levels mentioned above were found to be higher in the females with CP compared to the female healthy controls, we also compared these inflammation-related parameters of the males and females in the CP group to confirm that this difference stemmed from the females with CP. As above, Mann-Whitney U test was used for paired comparisons since the values did not exhibit a normal distribution.

Among the patients with CP, the plasma IL-1β (P=0.04, Fig 3A) and IL-9 (P=0.007, Fig 3C) levels were found to be significantly higher in the females (n= 15) compared to the males (n=15). But, there was no difference between male and female patients in terms of plasma IL-6 (P=0.165, Fig 3B), histamine (P=0.852, Fig 3D) and tryptase beta-2 (P=0.178, Fig 3E) levels.

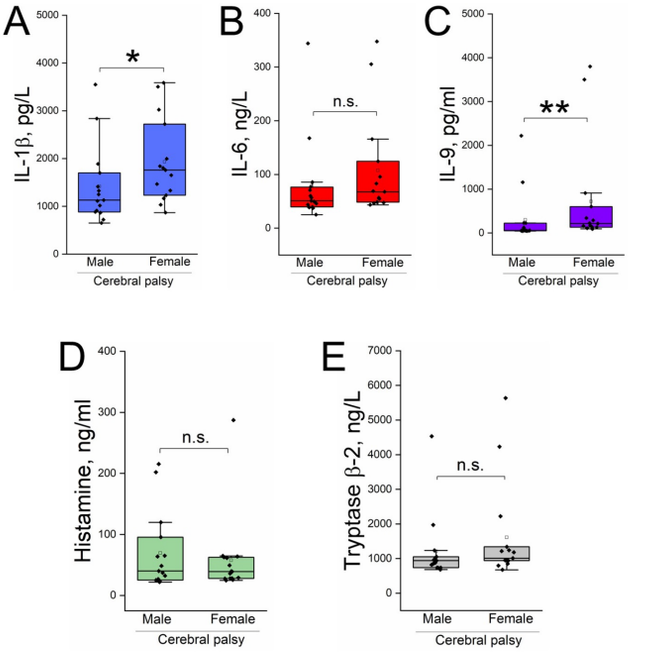

Figure 3. *High plasma IL-1β and IL-9 levels in females compared to males in the cerebral palsy group. Each box represents the median±SD, minimum and maximum values of the results. Plasma levels of these mediators between the cerebral palsy and control groups are compared by Mann-Whitney U test. n.s.: non-significance, *P < 0.05 and ** P < 0.01.*

3.4. Plasma proinflammatory cytokine levels and mast cell activation in patients with cerebral palsy by age groups (pre-adolescents and adolescents)

As a result of the analyses mentioned above, which indicated high levels of plasma proinflammatory cytokines and mast cell activation in females with CP, we asked the question of whether there was a difference according to pre-puberty and puberty periods. Accordingly, in order to find the answer to this question, we divided the male and female patients

in both groups into two subgroups as pre-adolescent (3-10 years of age, n=12 for control; n=17 for CP) and adolescent (11-17 years of age, n=14 for control; n=13 for CP) according to their developmental periods. Paired comparisons were compared using the Mann-Whitney U test since the data did not have normal distribution.

Among the female individuals, the plasma IL-6 (P=0.042, Fig 4B), IL-9 (P=0.043, Fig 4C) and histamine (P=0.041, Fig 4D) levels were found to be higher in patients with CP in the adolescence period compared to the healthy controls; however, no difference was found in terms of these parameters in the pre-adolescent period (P>0.05, Fig 4B-E). While plasma IL-1β levels were higher in patients with CP in pre-adolescence compared to the healthy controls (P=0.028, Fig 4A), no difference was found in terms of adolescent period (P>0.05, Fig 4A). Additionally, plasma tryptase beta-2 levels were not different in female patients with CP in neither pre-adolescence nor adolescent period compared to the healthy controls (P>0.05 for both comparisons, Fig 4E).

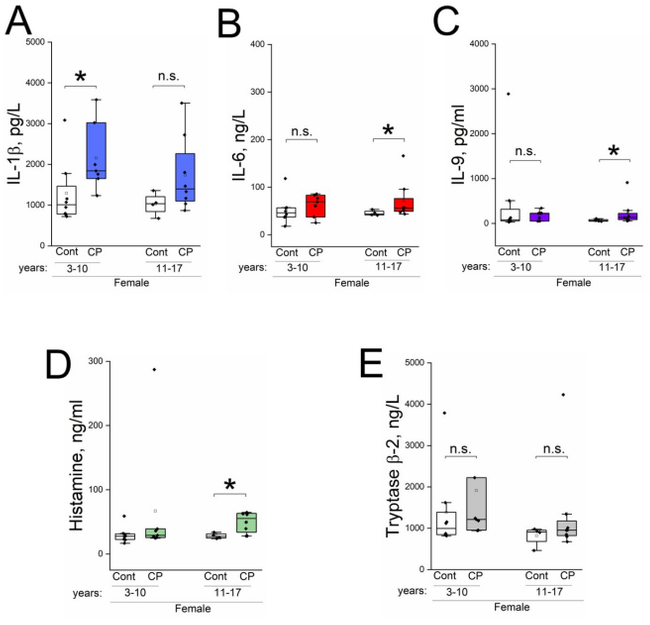

Figure 4. *High plasma IL-6, IL-9 and histamine levels in female subjects with cerebral palsy compared to healthy female controls in adolescence. Each box represents the median±SD, minimum and maximum values of the results. Plasma levels of these mediators between the cerebral palsy and control groups are compared by Mann-Whitney U test. n.s.: non-significance, *P < 0.05.*

On the other hand, unlike the females, no difference was found in male patients with CP in neither pre-adolescent nor adolescent period in terms of the plasma levels of IL-1β, IL-6, IL-9, histamine and tryptase beta-2 compared to the healthy controls (P>0.05 for all comparisons, Fig 5A-E).

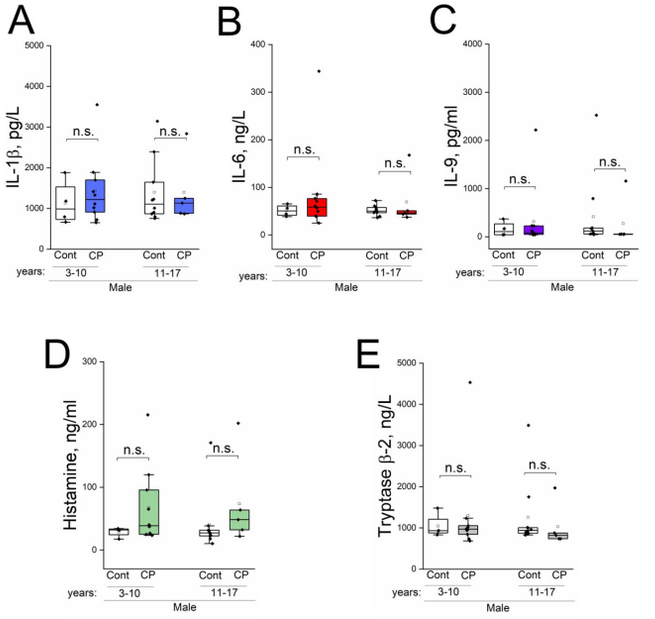

Figure 5. *Plasma levels of proinflammatory cytokines and mast cell mediators in male subjects with cerebral palsy by age periods. Each box represents the median±SD, minimum and maximum values of the results. Plasma levels of these mediators between the cerebral palsy and control groups are compared by Mann-Whitney U test. n.s.: non-significance.*

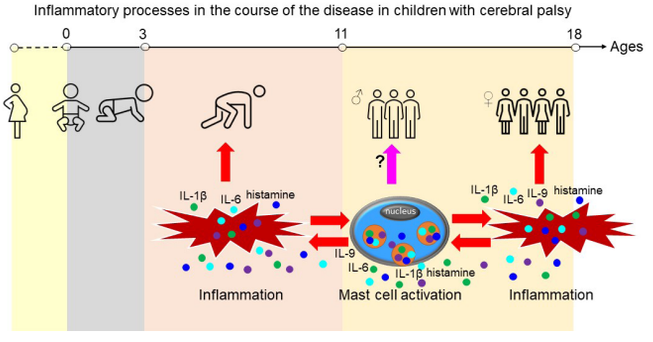

Figure 6. *Illustration of possible inflammatory processes in the course of the disease in children with cerebral palsy.*

4. DISCUSSION

The present study investigated the role of proinflammatory cytokines and immune mast cells in the course of the disease in children with CP between 3 and 18 years of age. The major findings of the study included higher plasma levels of proinflammatory cytokines IL-1β and IL-6, as well as histamine as a mast cell activation marker, in individuals with CP compared to the healthy controls. Moreover, it was found that these high inflammatory parameters in individuals with

CP stem from the females. The further analyses we made revealed that these high inflammatory values in female patients with CP were concentrated in the adolescent period, and they were rarely seen in the pre-adolescent period.

It is well known that abnormal expression of inflammatory cytokines can initiate perinatal brain injury in the pathogenesis of cerebral palsy (11-13). In addition to studies including the intrauterine period, it has been revealed that increased cytokine levels in neonatal blood at term delivery are strongly associated with the possibility of cerebral palsy (14,15).

Our findings revealed that the concentrations of proinflammatory cytokines IL-1β and IL-6, and the concentration of histamine as one of the mast cell activation markers, were higher in the plasma in patients with CP compared to the healthy controls. These findings are consistent with the results reported in the previous studies covering the intrauterine period or the period of early infancy before 2-3 years of age. In a previous clinical study, it was reported that the levels of proinflammatory cytokines IL-1β, IL-8, IL-9 and TNF-α in neonatal blood samples were higher in the group with CP compared to the controls (16). Similarly, in a clinical study conducted by taking blood samples of term infant with perinatal asphyxia, the levels of proinflammatory cytokines IL-1β, IL-6 and TNF-α were reported to be higher in children diagnosed with CP (17). In accordance with these studies, our findings have revealed that the increase in inflammatory cytokine levels plays an important role in both the pathogenesis and the course of the disease.

It is considered that proinflammatory cytokines such as IL-1β, which are released during the course of intrauterine infection, cause to the white matter damage in preterm infants developing CP (18). In the present study, the significantly higher plasma IL-1β, IL-6, and histamine concentrations of individuals with CP at 3-18 years of age compared to the healthy controls suggest that the increased inflammatory response still continues in childhood after 2 years of age, regardless of the initial trigger.

On the other hand, in our study, difference in the IL-9 levels was not statistically significant. This may be due to the fact that different proinflammatory cytokines may further come into prominence in the course of the disease in different age groups of children with CP. Moreover, gender difference may be another possible explanation of this. Because, in our study, plasma IL-9 concentration in the females with CP was found to be significantly higher compared to both the female healthy controls and the males with CP.

On the other hand, it is an important question whether there is a relationship between the gender difference and inflammatory processes that are effective in the course of CP. In the present study, plasma IL-1β and IL-9 levels were found to be higher in the females compared to the males among the patients with CP. Besides, interestingly, the plasma levels of IL-1β, IL-6, IL-9 and histamine were significantly higher in the females with CP compared to the female healthy controls; however, there was no difference between the males with CP and the males in the control group. These findings suggest that the increased inflammatory response, which plays a role in the course of CP in childhood after the age of 2, is more effective in female patients compared to the male patients; and in our findings, the major differences were due to mostly the female patients with CP.

Looking at the change of proinflammatory cytokine concentrations in female individuals by age groups, it was found that IL-6, IL-9 and histamine levels in females with CP were higher in the adolescents compared to the individuals of the same gender and age group in healthy controls. However, in females with CP, only IL-1β level in pre-adolescence period was higher compared to the healthy controls of the same gender and age group; and no difference was found in terms of other inflammatory parameters. Unlike females, no significant difference was found for any of these inflammatory parameters in males during the pre-adolescence or the adolescence period.

Estrogens whose levels begin to increase in adulthood may be responsible for the increase in inflammatory responses in the females with CP during adolescence. Because, estrogens are able to activate the mast cells (19). Activation of mast cells leads to induce inflammatory cascades. Mast cells can be activated by a large number of immunological and non-immunological agents (20,21). These include IgE, estrogen, and the inflammatory cytokines such as IL-1β, IL-3, IL-4, IL-9, IL-33 (19,21,22). It is well known that mast cell activation is increased in many inflammatory diseases (21,23). Consistent with this information, the high histamine levels found in patients with CP in our study indicated that the activation of mast cells were increased due to the increase of inflammatory cytokines (IL-1β, IL-6 and IL-9) in these patients.

On the other hand, in the present study, no difference was found between individuals with CP and the control group in terms of tryptase beta-2 levels, which are released from mast cells and accepted as an indicator of mast cell amounts. This finding suggests that mast cells play a key role in the course of the disease through their increased activation without changing in number.

In an experimental study mimicking hypoxic-ischemic brain injury in CP, IL-9 administration was reported to increase ibotenate-induced brain injury in normal mice, while no effect was observed on the mice genetically lacking mast cells (9). Moreover, it was demonstrated that a mast cell stabilizer cromolyn significantly reduced ibotenate-induced brain lesions (IL-9 treated) (10). In accordance with these studies, our study revealed that the mast cell activation plays an important role in the course of CP as in other brain injury models, and that this effect may continue in childhood.

5. CONCLUSION

Future clinical trials with mast cell stabilizers such as ketotifen and cromolyn may provide further information on whether

the mast cell stabilizers can be used to limit the inflammation in patients with CP.

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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