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Comparison of the serum cytokine levels before and after adrenocorticotropic hormone (ACTH) therapy in patients with infantile spasm

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ABSTRACT

Purpose: Infantile spasm is an age-dependent epileptic syndrome seen in infancy or early childhood. Although studies have investigated the epilepsy–cytokine relationship, there has been insufficient research into the relation between cytokines and infantile spasm. The purpose of this study was to examine the role of cytokines in the pathogenesis of infantile spasm by investigating cytokine levels before and 1 month after adrenocorticotropic hormone (ACTH) therapy in patients diagnosed with the condition.

Method: Twenty patients aged between 1 month and 2 years and diagnosed with infantile spasm at the Karadeniz Technical University Medical Faculty Department of Child Health and Diseases Pediatric Neurology Clinic, Turkey, and 20 healthy children were included in the study. Patients received 11 doses of ACTH on 2 days a week. Levels of TNF-alpha and IL-2, the main cytokines involved in inflammation and recently associated with infantile spasm, and of IL-1beta, IL-6 and IL-17A, associated with epileptic seizures, and serum levels of the IL-17A activator IL-23 were investigated in all patients at the start of treatment and 1 month after completion of treatment.

Results: No statistically significant difference was observed between pre- and post-treatment patient group and control group IL-1beta, IL-2, IL-23 or TNF-alpha levels. Pre-treatment IL-6 and IL-17A levels were significantly higher in the untreated patient group compared to the healthy control group ($p < 0.001$ and $p = 0.002$).

Conclusion: Our study supports the recent idea that IL-6 and IL-17A are cytokines involved in the pathogenesis of infantile spasm.

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1. Introduction

Infantile spasm, a childhood epilepsy with rather poor prognosis, is characterized by myoclonic seizures, a hypsarrythmic EEG pattern and developmental retardation. It was first described by William West in his own son in 1841. Various hypotheses have been proposed concerning the pathophysiology of infantile spasm. These include brain stem dysfunction due to pathology in serotonergic neurons, interaction between the brain stem and a focal or diffuse cortical abnormality, interaction between cortical–subcortical abnormalities and immunological dysfunction [1–4]. Changes in the hypothalamus-pituitary-adrenal axis have also been investigated, and it has been suggested that corticotropin releasing hormone (CRH) increases neuronal stimulability and seizures [5]. The hypothesis of a defect in the immune system in association with infantile spasm is based on studies showing the presence of antibodies forming against normal brain tissue in the sera of patients with infantile spasm, increased numbers of B and T cells in peripheral blood, and the presence of abnormal leukocyte antigen in patients compared to control cases [6,7]. However, there has been insufficient research into the relation between cytokines

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and infantile spasm. The purpose of this study was to examine the relation between infantile spasm-type seizures and cytokines and to determine whether, as predicted, cytokines are involved in the pathogenesis.

2. Materials and methods

Twenty patients aged between 1 month and 2 years presenting to the Karadeniz Technical University Medical Faculty Department of Child Health and Diseases Pediatric Neurology Clinic and diagnosed with infantile spasm and 20 age- and sex-matched healthy children were included in the study. Decimal age, age at onset of spasm, age at diagnosis, sex, characteristics of infantile spasm, pre-, natal and postnatal histories, family history, type of delivery, systemic and neurological examination findings, laboratory findings, cerebral imaging (magnetic resonance imaging – MRI) and electroencephalography (EEG) of all patients were investigated. Electroencephalography was performed using a 64-channel Nihon Kohden EEG device with an international electrode system. EEG was evaluated at the Department of Pediatric Neurology. Infantile spasm was diagnosed on the basis of flexor and extensor spasms recurring several times a day and lasting several seconds, hypsarrhythmia at EEG, and interrupted psychomotor development and/or retardation [8]. Hypsarrhythmia at EEG was defined as diffuse slow waves and suppression-burst findings in the form of spike-multiple spike activity or superimposed 'spike, multiple spike slow wave and subsequent suppression periods' [1]. The etiology of infantile spasm was classified under two main groups, symptomatic and cryptogenic, depending on the identification of a definable cause. Patients receiving corticosteroid derivative therapy in the previous 3 months, with accompanying adrenal or pituitary insufficiency, benign myoclonus of early infancy, tonic reflex seizures of early infancy, benign neonatal sleep myoclonus or benign and severe myoclonic epilepsy were excluded from the study. Patients received a total of 11 doses of ACTH (tetracosactide = Synacthen-Novartis depot vial) therapy on 2 days a week. Patients younger than 12 months received 0.5 mg (25 units) intramuscularly and those older than 12 months received 1 mg (50 units) intramuscularly. The ACTH dose was interrupted if side-effects of ACTH therapy, hyperactivity, hypertension, allergic reactions, infection or hypoglycemia, developed. Patients were divided into five groups based on their clinical response to treatment: complete response, temporary complete response, <50% decrease in spasms, >50% in spasms and no response.

Venous blood specimens were taken from all patients at the beginning and 1 month after completion of treatment in order to measure IL-1beta, IL-2, IL-6, IL-17a, IL-23, TNF-alpha levels. Specimens were centrifuged at 3000 rpm for 15 min for serum separation and were then stored at -80^0 C until analysis. Sera set aside for IL-1beta, IL-2, IL-6, IL-17a, IL-23 and TNF-alpha measurements were thawed at room temperature and studied using ELISA on the same day. The results were compared with those of a healthy age- and sex-matched control group. The control group was established following permission for additional blood collection from the families of healthy children of appropriate age attending our hospital's General Pediatric Department for check-up purposes and scheduled for blood tests. Approval for this was granted by the Karadeniz Technical University Faculty of Medicine ethical committee.

The study data were analyzed on SPSS (Statistical Package for the Social Sciences, version 20, SSPS Inc., Chicago, Ill, USA) software. Constant variables were expressed as 'mean ± standard deviation.' The Shapiro–Wilk test was used to determine compatibility with normal distribution of constant variables in the data set. The '*t* test for dependent groups' was used to compare normally distributed constant variables and the '*t* test for independent groups' to compare independent variables. The 'Wilcoxon signed ranks test' was used to compare non-normally distributed dependent constant variables and the 'Mann Whitney *U* test' to compare independent constant variables. The 'chi square test' (χ^2) was used to test the presence of relations between categoric variables. Relations between constant variables were also examined using the 'Spearman rank correlation test.' *p* values of less than 0.05 were considered significant for all test results.

3. Results

The etiology of infantile spasm was determined to be symptomatic in 7 (35%) patients and cryptogenic in 13 (65%). Prematurity was present in 1 (14%) of the patients in the symptomatic group, Hypoxic ischemic encephalopathy in 5 (71%) and congenital CMV infection in 1 (14%). EEG was performed at time of diagnosis in all patients. A classic hypsarrhythmia pattern was determined in 12 (60%) and a modified hypsarrhythmia pattern in 8 (40%). Cerebral imaging was performed in all cases. No pathological finding was determined in 13 (65%) cases, while pathological MRI findings (multicystic encephalomalacia, cerebral atrophy, periventricular leukomalacia and hypoxic injury) were identified in 7 (35%).

No significant differences were determined at comparison of pre-and post-ACTH therapy serum **IL-23**, TNF-**alpha, IL-2 and IL-1beta** levels and those of the healthy control group (Table 1).

Serum **IL-6** levels decreased following ACTH therapy, although this was not statistically significant. However, comparison of patients' pre-treatment IL-6 levels and those of the healthy control group revealed significant elevation in the patient group ($p < 0.001$) (Table 1). Additionally, a significant correlation was determined between a decrease in IL-6 levels and type of infantile spasm. The decrease in IL-6 levels in the cryptogenic group was significantly greater than that in the symptomatic group ($p = 0.044$).

Table 1
Comparison of the pre-treatment and post-treatment groups and the pre-treatment and control groups.

		Pre-treatment	Post-treatment	*p*
IL-1β	Patient group	16.82 ± 22.08	13.78 ± 10.66	0.985[a]
	Control group	22.02 ± 24.48		
	p	0.705[b]		
IL-2	Patient group	24.86 ± 15.55	24.49 ± 14.32	0.946[c]
	Control group	17.63 ± 10.80		
	p	0.245[b]		
IL-6	Patient group	94.42 ± 60.37	62.36 ± 58.39	0.086[a]
	Control group	33.97 ± 34.32		
	p	0.001[b]		
IL-17A	Patient group	1.13 ± 0.74	0.83 ± 0.64	0.215[a]
	Control group	0.61 ± 0.54		
	p	0.002[b]		
IL-23	Patient group	36.11 ± 40.91	40.16 ± 27.05	0.433[a]
	Control group	42.63 ± 26.15		
	p	0.140[b]		
TNFα	Patient group	14.68 ± 8.06	12.62 ± 6.73	0.313[a]
	Control group	15.62 ± 11.50		
	p	0.957[b]		

[a] Pretreatment group compared with postreatment group – Wilcoxon test.
[b] Patients compared with control group – Mann Whitney *U* test.
[c] Pretreatment group compared with postreatment group for IL-2 – Paired *t* test.
Presence of differences in parameters between the patient and control groups was tested using the Man Whitney *U* test ([b]) since the data were not normally distributed. Since IL -2 was normally distributed the presence of a difference before and after treatment in the patient group was investigated using the Paired *t* test ([c]), while other parameters were compared using the Wilcoxon test ([a]) since these were not normally distributed.

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