Immunologic Evaluation in the Patients with Infantile Spasm

İnfantil Spazmlı Hastaların İmmünolojik Değerlendirilmesi

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ABSTRACT Objective: The aim of the present study was to investigate the etiologic factors and immunological findings in the patients with infantile spasm (IS). **Material and Methods:** Twenty-five infants (17 boys, 8 girls) with IS were included in the study. The clinical characteristics and underlying etiologic factors were analyzed. Neurometabolic and immunologic tests, neuroimaging and electroencephalography were performed. Twenty healthy infants were chosen as the control group. The groups were compared regarding serum immunoglobulin levels, complement proteins and T lymphocyte subgroups. **Results:** The male/female ratio was 2/1 and mean age was 8.6±3.5 months in patients with IS. Most (88%) of the patients with IS were classified as structural/metabolic, the most frequent etiological factor being hypoxic-ischemic encephalopathy. Cerebral infarct, tuberous sclerosis, cortical dysplasia and metabolic diseases were other causative factors. All patients received adrenocorticotrophic hormone as first line treatment except two patients with tuberous sclerosis treated with vigabatrin. The patients with IS had lower median IgA, IgM, IgG, C3 and C4 levels compared to healthy control group. The distribution of lymphocyte subgroups CD3+,CD4+,CD8+ and CD19+ were not different between two groups. **Conclusion:** Humoral and cell-mediated components of the immune system can be affected in IS. This may be due to the underlying brain disorder or to seizures, and may suggest inflammatory mechanisms taking part in IS. Immune dysregulation should be taken into consideration when treating IS.

Key Words: Spasms, infantile; lymphocyte subsets; immunoglobulin A; immunoglobulin G; immunoglobulin M; complement C3; complement C4

ÖZET Amaç: Bu çalışmanın amacı infantile spazmlı hastalarda etiolojik faktörleri ve immünolojik bulguları araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya infantile spazmlı 25 süt çocuğu (17 erkek, 8 kız) dahil edildi. Klinik özellikleri ve altta yatan etiolojileri analiz edildi. Nörometabolik, immünolojik, nörogörüntüleme testleri ve elektroensefalografi uygulandı. Yirmi sağlıklı infant kontrol grubu olarak seçildi. Gruplar serum immünoglobulin,kompleman düzeyleri ve T lenfosit alt gruplarına göre karşılaştırıldı. **Bulgular:** Erkek/kız oranı 2/1 ve hastaların ortalama yaşı 8,6±3,5 aydı. Hastaların (%88) çoğu yapısal/metabolik olarak sınıflandırıldı, en sık etiyolojik faktör hipoksik iskemik ensefalopatiydi. Serebral infarkt, tuberoskleroz, kortikal displazi ve metabolik hastalıklar diğer sebep olan faktörlerdi. Vigabatrinle tedavi edilen iki tuberosklerozlu hasta dışında bütün hastalar ilk basamak olarak adrenokortikotrofik hormon tedavisi aldılar. İnfantil spazmlı hastalar kontrol grubundan daha düşük ortalama IgG, IgM, IgA, C3 ve C4 değerlerine sahipti. CD3+, CD4+, CD8+ ve CD19+ lenfosit alt grupları dağılımı iki grup arasında farklılık göstermemekteydi. **Sonuç:** Humoral ve hücresel immün sistem, infantil spazmda etkilenmektedir. Bu altta yatan beyin bozukluklarına veya nöbetlere bağlı olabilmekte, ve infantil spazmda yer alan inflamatuar mekanizmaları akla getirmektedir. İmmün disregülasyon infantil spazmlı hastaların tedavisinde dikkate alınmalıdır.

Anahtar Kelimeler: Spazm, bebek; lenfosit alt grupları; immünoglobulin A; immünoglobulin G; immünglobulin M; kompleman 3; kompleman C4

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Infantile spasm (IS) is an epileptic syndrome of infancy with the typical symptom of flexor or extensor spasms occurring in clusters and starting under 2 years of age. The interictal electroencephalography (EEG) demonstrates hypsarrhythmia or 'modified' hypsarrhythmia.[1]

This syndrome was classified into two groups: symptomatic and cryptogenic. Symptomatic IS is characterized by the presence of previous signs of brain damage (psychomotor retardation, neurological signs, radiological signs or other types of seizures) or by a known etiology. The cryptogenic group has normal development until the beginning of spasms, and no etiology can be demonstrated. However, International League Against Epilepsy (ILAE) recommended a new classification system with the following terms 'Genetic', 'Structural/metabolic' and 'Unknown' instead of the terms idiopathic, symptomatic and cryptogenic in 2010. The concept of genetic epilepsy is the direct result of a known or presumed genetic defect in which seizures are the core symptom of the disorder. In the structural/metabolic group, there is a distinct structural (acquired disorders such as stroke, trauma and infection) or metabolic condition or disease (tuberous sclerosis, malformation of cortical development) that has been demonstrated to be associated with an increased risk of developing epilepsy. 'Unknown' is meant to designate that the nature of the underlying cause is yet unknown.[2]

The pathophysiological mechanisms of IS remain poorly understood. Significant progress has been made towards the identification of specific genes: ARX, CDKL5, PAFAH1B1/LIS1, DCX, FOXG1, GRIN1, GRIN2A, MEF2C, TSC1 and TSC2.[3] Beside genetic factors and structural anomalies, various perinatal central nervous system (CNS) problems like hypoxic-ischemic injury, intrauterine or postnatal infections, stroke or trauma have been demonstrated as causative factors for IS. The common clinical and EEG features resulting from these various factors suggest that their pathogenesis involves a final common pathway which may involve immunological mechanisms.[4] A bidirectional modulation exists between the nervous and immune systems: neural and immune cells interact to regulate inflammation and function in the CNS.[5] Immune mechanisms may underlie or aggravate certain types of epilepsy, as supported by elevated levels of proinflammatory agents in children with epilepsy, the presence of chronic inflammation in Rasmussen encephalitis (RE), the high incidence of seizures in autoimmune diseases, the recently described group of autoantibody-mediated epileptic encephalopathies and the beneficial effects of steroids and other anti-inflammatory treatments in some drug-resistant epilepsies.[6-11] The latter has classically been considered as supportive of inflammatory or immune-mediated pathogenesis. Independent of etiology, IS patients benefit from steroid and adrenocorticotrophic hormone (ACTH) treatment. Immunologic mechanisms in IS are supported by increased IL-2, TNF-α and INF-α in cryptogenic and symptomatic IS, altered levels of immunoglobulins, presence of immature thymocytes in peripheral blood, functional impairment of T lymphocytes induced by plasma inhibitory factors, and increased levels of serum interleukin-1 receptor antagonist subsequent to resolution in clinical and EEG findings.[12-14]

From this point of view, we simply hypothesized that; if there is a final common pathway involving immunological processes, we should find immunologic alterations in our patients with IS. Thus, we investigated the immunologic and clinical characteristics of a group of patients with IS.

MATERIAL AND METHODS

Twenty-five infants (17 boys and 8 girls) newly admitted with IS to Ankara Children's Health and Diseases Hematology-Oncology Education and Research Hospital between January 2008 and January 2010 were included. The structural/metabolic or unknown groups were determined after the diagnostic work-up. Gender, age at onset, systemic and neurological examinations, prenatal, natal and postnatal history, family history of epilepsy and febrile seizure were analyzed. All patients underwent magnetic resonance imaging (MRI). Neurometabolic investigations including serum and urine amino acids, urine organic acids, serum acylcarnitine profile, pyruvate, lactate and ammonia levels, bio-

tinidase activity, and routine karyotyping was performed. Repeated ictal and interictal EEG recordings were obtained. Serum immunoglobulins (IgG, IgM, IgA) and complement components C3, C4 were analyzed quantitatively by nephelometry (IMMAGE 800, Beckman Coulter Nephelometer, USA), and lymphocyte subpopulation CD3+, CD4+, CD8+, CD19+ percentages were analyzed by flow cytometry (FACScalibur, Beckton-Dickinson, USA). All blood samples were collected before starting ACTH treatment. The control groups consisted of 20 patients with afebrile convulsions (AC) (12 idiopathic, 8 symptomatic) and 20 healthy infants (HC) followed in the Well Child Clinic of the same hospital and who underwent blood sampling for other reasons. The study was approved by the institutional ethical committee.

Immunological variables in the patient and control groups were compared using Mann-Whitney U test. Continuous variables were expressed as median (min-max) and mean ± standard deviation. The frequencies were shown as percentage. A p value<0.05 was considered statistically significant. Statistical comparisons were made using SPSS for Windows 15 package program.

RESULTS

CLINICAL CHARACTERISTICS

The male-to-female ratio was 2:1 and mean age of onset was 8.6±3.5 months in the IS group. The mean age in HC group was 10.1±4.0 months. There was no significant difference regarding age and gender between two groups.

The mean value of delay between the onset of IS and admission was 39 days. Twenty-two patients (88%) had structural/metabolic diseases and 3 (12%) patients were in the unknown group. The most frequent etiological factor was hypoxic-ischemic encephalopathy (n=15, 60%). Two infants suffered from tuberous sclerosis. Cerebral infarct (2), cortical dysplasia (1) and metabolic diseases (2) were other causative factors. Five patients had been receiving antiepileptic drugs (phenobarbital, carbamazepine, or valproate) for the diagnosis of seizures before the onset of the IS.

Two IS patients had a first-degree relative with a history of epilepsy, and one had a first-degree relative with a history of febrile seizure. Three infants were products of a consanguineous marriage. Neurometabolic investigations allowed the diagnosis of mitochondrial cytopathy and neurotransmitter disease in two patients. In one patient, two mutations in the SCN1B gene were found.

EEG recordings were performed in all patients at the time of diagnosis. Typical or modified hypsarrhythmia was seen in 22 and 3 patients respectively.

Cranial MRI revealed various findings in the structural/metabolic group: encephalomalacia, cerebral atrophy, infarcts, cortical tubers, dysplasia, periventricular leukomalacia, corpus callosum dysgenesis, or symmetrical signal changes in basal ganglia. Cranial MRI findings were normal in unknown group.Visual evoked potentials were abnormal in 18/25 and brainstem auditory evoked potentials in 3/25 patients.

The first-line medication for 23 patients was synthetic ACTH 50 U/day, intramuscular, two times a week (tetracosactide, Synachten Depot 1mg/mL) and pyridoxine (125mg/day, oral). Patients with tuberous sclerosis were treated with vigabatrin only. Vigabatrin was added as a second-line therapy in four infants who did not respond to ACTH. Spasms subsided completely after treatment in all 25 children. A repeat EEG was performed after eight doses of ACTH and disappearance of hypsarrhythmia was observed in all patients.

IMMUNOLOGICAL VARIABLES (TABLES 1, 2):

Patients with IS had lower IgG, IgM and IgA levels compared to HC (p=0.077, 0.015 and 0.014, respectively). The complement protein C3 and C4 levels were significantly lower than HC group (p<0.001). The mean percentage of CD3+ and CD4+ lymphocyte subsets were lower than control groups (CD3+ 56.2 % vs 66.1%, CD4+ 34.7% vs 41.2%). Among lymphocyte subgroups, total CD3+ and CD4+ lymphocyte counts in IS were lower than HC, but there was no significant difference statistically. The distribution of lymphocyte subgroups CD8+ and

CD19+ were not different between two groups. The median, minimum and maximum levels of Ig, complement and T lymphocyte subgroups with p value are shown in Tables 1, 2.

DISCUSSION

Interest in the relationship between epilepsy and the immune system has been increasing in recent years. Most studies concentrated on inflammatory mediators and particularly cytokines as contributors to seizure predisposition and seizure-related brain injury.[15] We investigated immunoglobulins, complement and cell-mediated immune response in IS. We found median IgG, IgM and IgA levels lower in IS supporting the idea that IS is associated with disturbances in humoral immunity. Six patients with IS had hypogammaglobulinemia (three with low IgG, one with low IgA and two with low IgA, IgG, IgM). The low levels in IS seem to be due to transient hypogammaglobulinemia of infancy, but this diagnosis can only be confirmed by resolution by 30-40 months of life.[16] Low serum concentrations of IgA have been reported due to antiepileptic treatment but a few studies found low IgA levels in epileptic patients. Eeg-Olofsson et al. found low serum IgA in patients with focal, mainly temporal lobe epilepsy and lower levels of IgA (23.9%) were detected in another study consisting of the patients with IS and Lennox-Gastaut syndrome.[17-19] Because most of our IS cases were in the structural/metabolic, the etiological condition; hospitalization and nutritional deficiency due to hypoxic-ischemic encephalopathy, prematurity, and metabolic disorders could have resulted in immune disturbances (Table 1). The previous antiepileptic treatment of our 5 IS cases consisted of phenobarbital (3), carbamazepine (1) and valproic acid (1). The use of carbamazepine and valproic may be associated with a significant decrease in IgA levels, but no relationship has been reported between phenobarbital and immunoglobulin levels.[18] Several patients in the structural IS group had infectious diseases such as sepsis, neonatal pneumonia, viral encephalitis, acute pyelonephritis, and thismight be associated with low Ig levels: 7 patients had gram (-) infections with E.coli and Klebsiella recovered in blood and urine cultures before the occurrence of the spasms. Bacterial lipopolysac- charides (LPS) can activate Toll-like receptor 4 (TLR4), whose signaling has been reported to promote epileptogenesis.[20] Galic et al. showed that a single LPS injection during a critical postnatal period causes a long-lasting increase in seizure susceptibility in rats.[21] Brief systemic inflammation during critical periods of development, even when not associated with obvious CNS injury, may result in vulnerability of the CNS.[21]

TABLE 1: Serum immunoglobulin (Ig) and complement protein levels in patient and control group (median, min-max value).

Ig levels (mg/dL)	IS (n=25)	Control (n=20)	p value
Ig G	517 (217-1290)	652 (471-991)	0.077
Ig A	25 (12-158)	44.5 (16-104)	0.014
Ig M	64 (19-139)	90 (34-243)	0.015
C3	98 (47-169)	137 (96-176)	<0.001
C4	18 (14-31)	38 (22-52)	<0.001

TABLE 2: Total T lymphocyte subset counts in the patient and the control groups (median, min-max).

Lymphocyte subsets	IS (n=25)	Control (n=20)	p value
CD 3+	2160 (450-8036)	2388 (1012-5076)	0.819
CD 4+	1260 (288-6199)	1354 (298-3672)	1.000
CD 8+	768(126-1900)	786 (529-3672)	0.591
CD19+	1001(356-4936)	1005(428-2300)	0.784

The complement proteins C3 and C4 have been examined in relation with epilepsy but not with IS. The complement system plays a protective role in inflammation by clearing cell debris after injury, but may have potential adverse effects: the complement cascade has been involved in the pathogenesis of both experimental and human temporal lobe epilepsy and in Rasmussen's syndrome.[22-24] The progressive neurologic deterioration, complement activation and the efficacy of anti-inflammatory treatment are common findings observed in IS and RE. In our study, C3 and C4 levels tended to be low in IS. This may be due to consumption after activation of the complement cascade, to immunosuppression due to stress response or to the etiological factors in IS leading to

hypocomplementemia as well as hypogammaglobulinemia. Prematurity, malnutrition, acute bacterial infections, specifically Gram (-) infections, inflammatory diseases are known to be associated with hypocomplementemia. Stress and corticotropin releasing hormone (CRH) influence TH1 and TH2 immune responses by stimulating glucocorticoid, catecholamine and peripheral (immune) CRH secretion and by altering the production of key regulatory cytokines and histamine. Stress hormones selectively suppress TH1 responses and favor TH2 responses.[25] Taken together, reduced immunoglobulins and complement activation might be related to an inflammatory process resulting in epileptogenesis in IS.

CD3+ and CD4+ T cells were low in our IS group. Montelli et al. reported a significant reduction in the proportion of CD3+ and CD4+ T cells and an increase in CD8+ cells patients with IS but also with Lennox-Gastaut syndrome and epilepsy with multifocal independent spikes: the CD4+/CD8+ ratio was below 2 SD of the control group in 81% of the patients.[13] A low CD4+/CD8+ ratio has been reported in focal and generalized epilepsies.[19] Liu et al. found significantly higher IL-2, TNF-α and IFN-α levels in both cryptogenic and symptomatic WS patients compared to the control group.[12] Yamanaka et al. evaluated whether proconvulsive interleukin-1β (IL-1β) and anticonvulsive IL-1 receptor antagonist (IL-1Ra) were markers of the effectiveness of treatment in patients with West syndrome (WS).[14] They showed that serum IL-1Ra levels were elevated subsequent to resolution of clinical and EEG findings in WS patients. These studies support the idea that an imbalance in cytokine levels may be involved in the immunopathology of WS.

These findings may be secondary to the etiological condition or to the seizures themselves, as for other immunological parameters, neurotransmitters, cytokines or hormones, may affect lymphocyte subgroups. In our study, the IS group had altered lymphocyte counts. This may be an effect specific for this type of epilepsy in this age group.

Because the immunologic abnormalities were observed more prominently in the symptomatic group, the alterations in the immune system are likely to be related to the underlying brain lesions or injury. Bilateral brain lesions modulate the immune responses in rodents. Cellular immune responses, CD4+ helper lymphocyte population, and antibody synthesis are impaired in animals lesioned in the locus ceruleus.[26] Lesions of right or left neocortex induce opposite effects on various immune parameters including lymphocyte proliferation to mitogens, production of interleukin-2, macrophage activation, and natural killer cell activity.[27] IS is usually a CNS dysfunction associated with generalized EEG abnormalities and disturbance of centrencephalic regions may affect immunomodulation.

A genetic abnormality causing simultaneous dysregulation of the immune and the nervous systems is unlikely because of the various etiologies included in our series and various types of epilepsy included in reports from the literature. One patient with IS had mutation in the SCN1B gene (Thr35Ser aa in exon 2 and Leu210Pro aa in exon 3). The SCN1B gene does not have any known interaction with the immune system genes. One of our IS patients had been treated with interferon-α (IF-α) for hemangioma at 2 months of age but treatment was withdrawn because of fever resistant to antipyretics. Generalized tonic-clonic convulsions and IS developed at 6 and 11 months of age, respectively. Seizures during treatment with IF-α have been reported, possibly due to lowered epileptic threshold by the drug.[28] Interestingly, we did not find any report on a relationship between IF-α and occurrence of IS. We included these patients into 'unknown' group as any report has not been published showing the relationship between SCN1B-IS or IFα-IS.

The abnormalities in humoral and cell mediated immune responses observed in IS might be of importance in terms of further treatment. The effect of ACTH in IS has been explained by the epileptogenic effect of CRH being inhibited by exogenous ACTH.[29] Two studies in our country supported that ACTH is the most effective therapy in the treatment of IS.[30-31] ACTH and steroids may accelerate brain maturation and this may explain

their efficacy in an age-related syndrome such as IS. However ACTH affects the immune system. Shiihara et al.measured peripheral lymphocyte subset and serum cytokine profiles and compared the results between before (pre-ACTH) and after (post-ACTH) ACTH and also compared these results with control group.[32] They showed that CD3+,CD25+cells,CD19+ cells and CD19+cells and CD19+CD95+ cells decreased in the pre-ACTH group as compared to the controls. CD3+CD25+ cells comprehend regulatory T-cells (Tregs) which are essential for maintaining peripheral tolerance, preventing autoimmune diseases and limiting chronic inflammatory diseases. The reduced levels of CD19+CD95+ cells could indicate reduced B-cell apoptosis in the pre-ACTH group. B-cell apoptosis plays an important role in the elimination of self-reactive B-cells, and also B cells play a pivotal role in some autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. The elevations of IL-5 and IL-6 also indicated T cell activation. They suggested that T-cell and B-cell activation have some role in WS, and ACTH therapy might associate with T-cell inactivation. ACTH and other melanocortin peptides reduce production of proinflammatory cytokines and chemokines (IL-1, IL-8, TNF-α) and other mediators of inflammatory processes (NO, adhesion molecules).[33] ACTH exerts immunomodulatory effects by affecting T cell functions inducing expression of Treg cells, increased secretion of immunoregulatory IL-4 and decreasing IL-17, IL-2 and IFN-γ in CNS lymphocytes in studies on experimental autoimmune encephalomyelitis (EAE,a mouse model for MS).[34] The similar mechanisms might play a role in the treatment of the patients with IS by ACTH.

ACTH therapy may cause severe lymphopenia especially in the CD3+ and CD4+ lymphocyte subgroups.[35] Patients with low counts in the beginning of treatment would require closer follow-up for infections. In our experience, two patients (not included in the current study) who had recurrent infections in the presence of low CD3+ counts were treated successfully with ACTH administered with prophylactic trimetoprim-sulfamethaxazole and fluconazole to prevent infections.

In conclusion, immune system alteration seems to be involved in the pathophysiology of IS.

Our results provide further support to humoral and cell-mediated immune response changes occurring in IS and hypocomplementemia is a new finding in IS patients which has not been mentioned in the literature before. This may support the idea that complement activation might be related to an inflammatory process resulting in epileptogenesis in IS. The associations of SCN1B-IS and IFα-IS are also interesting findings which have not been published in the literature. The genetic factors or environmental influences seem to trigger immunologic mechanisms and result with a 'final common pathway' causing common clinical and EEG features. Care and follow-up of immunologic parameters are required during administration of immunosuppressive treatments and certain antiepileptic drugs in the patients with IS.

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