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Nerve Growth Factor (NGF) Levels in Generalized Epilepsy and Their Association with Cognitive Impairment and Affective Symptoms

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Abstract Epilepsy is a chronic neurological disorder often accompanied by cognitive impairment and affective disturbances in addition to recurrent seizures. Neurotrophic factors, particularly nerve growth factor (NGF), play an important role in neuronal plasticity and cognitive functioning, but their role in generalized epilepsy remains insufficiently studied. The aim of this study was to evaluate plasma NGF levels and their association with cognitive impairment and depressive symptoms in patients with generalized epilepsy. A total of 83 patients with epilepsy and 15 healthy controls were examined. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), affective symptoms using the Hospital Anxiety and Depression Scale (HADS), and plasma NGF levels were measured by ELISA. Cognitive decline was associated with longer disease duration ($p = 0.023$) and higher seizure frequency ($p = 0.002$). NGF levels decreased with increasing disease duration ($p < 0.001$) and showed a positive correlation with cognitive performance ($p = 0.007$), but were not significantly associated with anxiety or depression scores. Reduced NGF levels may reflect impaired neurotrophic support and could be related to cognitive dysfunction in generalized epilepsy.

Keywords Generalized epilepsy, Cognitive impairment, Depression, Nerve growth factor (NGF), Neurotrophic factors, MoCA, HADS, Seizure frequency

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent epileptic seizures, which represent its main clinical manifestation. Epileptic seizures arise from abnormal, excessive, or synchronous electrical activity of neuronal networks in the brain and may present as transient motor, sensory, autonomic, cognitive, or consciousness disturbances [2]. In modern epileptology, epilepsy is no longer considered a condition limited to seizures alone, but rather a complex clinical-neurobiological syndrome characterized by a persistent predisposition to generate epileptic seizures [3].

Clinically, epileptic seizures are highly heterogeneous and may manifest as brief impairment of consciousness (absence seizures), myoclonic phenomena, focal motor or sensory symptoms, or generalized tonic–clonic convulsions involving the entire body [4]. Importantly, the clinical consequences of epilepsy are not restricted to seizures. The disorder is frequently associated with cognitive impairment, affective disturbances (anxiety and depression), difficulties in social adaptation, and reduced quality of life [5].

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The pathogenesis of cognitive and affective disturbances in epilepsy involves dysfunction of frontal–thalamo–cortical networks, imbalance between GABAergic and glutamatergic neurotransmission, neuroinflammatory processes, and alterations in neurotrophic factors [8]. In particular, changes in the levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been shown to influence synaptic plasticity, neuronal survival, and emotional regulation [1,6]. Decreased NGF levels observed in both depression and epilepsy suggest the presence of shared pathophysiological mechanisms underlying these conditions [7,9].

In generalized epilepsy, cognitive and affective disorders are often underestimated in routine clinical practice. However, early detection and regular monitoring of these disturbances are essential for improving quality of life, enhancing treatment adherence, and optimizing disease prognosis. Therefore, the use of validated screening tools such as the Montreal Cognitive Assessment (MoCA) and the Hospital Anxiety and Depression Scale (HADS) should be considered an integral part of the comprehensive evaluation of patients with generalized epilepsy [10,11]. MoCA and HADS scales provide convenient and reliable instruments for the complex assessment of cognitive and affective disturbances in patients with generalized epilepsy.

Therefore, the aim of this study was to investigate plasma NGF levels and their association with cognitive impairment and affective symptoms in patients with generalized epilepsy.

2. Material and Methods

Patients for the study were selected from the clinical base of the Tashkent City Clinical Hospital No. 7, and laboratory investigations were performed at the scientific laboratory of the Tashkent State Medical University. The study was conducted between 2024 and 2025.

A total of 83 patients with epilepsy were included in the study. Diagnosis of epilepsy was confirmed based on clinical evaluation and electroencephalography (EEG) findings according to ILAE recommendations. According to seizure type, the main group consisted of 46 patients with generalized epilepsy (GE), including 7 patients with juvenile absence epilepsy (YAE), 12 patients with juvenile myoclonic epilepsy (JME), and 27 patients with generalized tonic-clonic seizures (GTCS). The comparison group included 37 patients with focal structural epilepsy (FE). The control group consisted of 15 age-matched healthy volunteers (e.g. Figure 2.1).

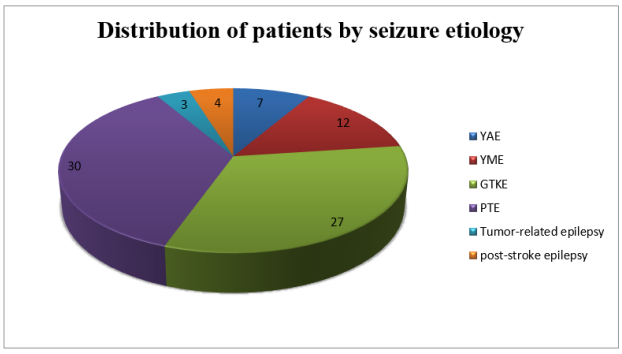

Figure 2.1. Distribution of patients by seizure etiology

This was a cross-sectional observational study. Patients were divided into three groups:

1) Main group – generalized epilepsy (n=46)
2) Comparison group – focal epilepsy (n=37)
3) Control group – healthy individuals (n=15)

Subgroup analysis in the main group was performed based on clinical severity (1a–1c).

The following parameters were assessed:

- Cognitive function (MoCA)
- Affective status (HADS-A, HADS-D)
- Plasma NGF levels (ELISA)
- Clinical variables (disease duration, seizure frequency)

2.1. Inclusion Criteria

Patients were included in the study according to the following criteria:

- Age ≥ 18 years
- Diagnosis of epilepsy confirmed according to ILAE criteria
- Presence of generalized tonic-clonic seizures
- Duration of epilepsy ≥ 1 year
- Blood samples obtained in the postictal period (at least 3 days after the last seizure)
- Written informed consent obtained from the patient

2.2. Exclusion Criteria

Patients were excluded from the study if any of the following conditions were present:

- Patients with severe depression were excluded based on HADS-D scores ≥11, in accordance with standard interpretation guidelines.
- Pregnancy or breastfeeding
- Epilepsy caused by infectious or autoimmune diseases of the central nervous system
- Recent use of immunomodulators, glucocorticoids, or other therapies that may affect neurotrophic factor levels

All patients underwent a standard neurological examination. Cognitive functions were evaluated using the Montreal Cognitive Assessment (MoCA), which assesses attention, executive functions, memory, language, abstract reasoning, visuospatial abilities, and orientation.anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Blood samples were obtained at least 3 days after the last seizure. Plasma was separated and nerve growth factor (NGF) levels were determined using an enzyme-linked immunosorbent assay (ELISA).

The mean age of patients was 35.93 ± 11.67 years in the generalized epilepsy group, 42.24 ± 11.79 years in the comparison group, and 37.53 ± 12.25 years in the control group. A total of 51 patients (61.44%) were male and 32 (38.55%) were female.

3. Results

In this study, cognitive function in patients with generalized epilepsy was assessed comprehensively. Cognitive impairment was detected in the majority of participants. Mild cognitive impairment was observed in 78 patients (79.5%), normal cognitive function in 14 patients (14.3%), and moderate cognitive impairment in 6 patients (6.2%). These findings suggest that long disease duration and recurrent seizures may be associated with neurofunctional changes.

According to MoCA scores, ≥26 points were considered normal, 18–25 points as mild cognitive impairment, and ≤17 points as moderate cognitive impairment. Figure 3.1 shows the distribution of MoCA scores at baseline in the main (1a–1c), comparison, and control groups, presented as a box plot.

In the main group, cognitive decline was closely associated with the clinical course of epilepsy. Greater cognitive impairment was observed in patients with longer disease duration and higher seizure frequency, suggesting a cumulative negative effect of chronic epileptic activity on brain functional systems.

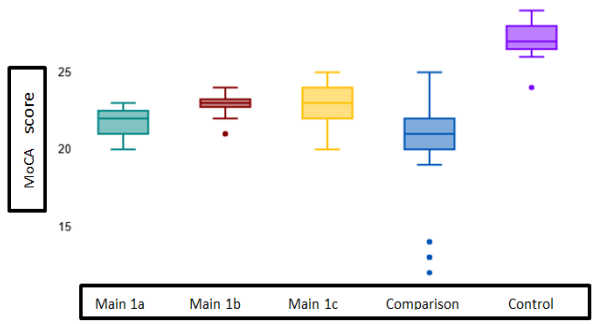

Figure 3.1. Distribution of MoCA scores in the main, comparison, and control groups

A weak but statistically significant negative correlation was found between disease duration and MoCA scores ($r = -0.34$; $p = 0.023$), indicating a tendency toward cognitive decline with longer epilepsy duration. A moderate and statistically significant negative correlation was also observed between seizure frequency during the last 6 months and MoCA scores ($r = -0.46$; $p = 0.002$), confirming that more frequent seizures are associated with worse cognitive performance. Overall, seizure frequency appeared to be a stronger determinant of cognitive impairment than disease duration.

In the comparison group, cognitive impairment was mainly related to the underlying structural brain damage. In some cases, cognitive decline persisted despite adequate seizure control. No significant correlation was found between baseline MoCA scores and disease duration ($r = -0.06$; $p = 0.744$) or seizure frequency ($r = -0.06$; $p = 0.714$), indicating that cognitive function in this group was not significantly associated with clinical characteristics of epilepsy.

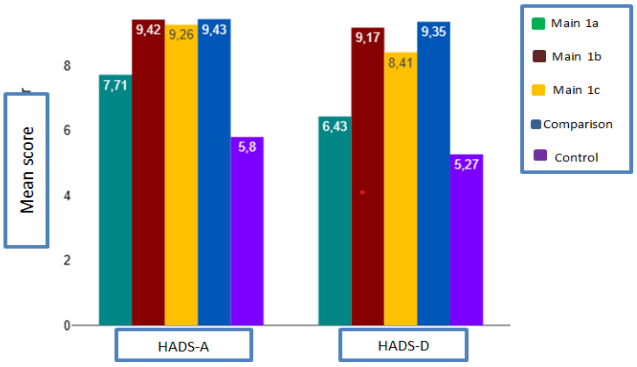

Figure 3.2. HADS-A and HADS-D scores in the main, comparison, and control groups

Based on baseline assessment, depressive and anxiety symptoms were analyzed separately in the main and comparison groups (e.g. Figure 3.2). Emotional disturbances were observed in both groups, although their severity differed.

In the main group (n = 46), the mean HADS-D score was 8.30 ± 1.62, corresponding to mild depressive symptoms. In the comparison group (n = 37), the mean HADS-D score was 9.35 ± 1.49, indicating a relatively higher level of depressive symptoms compared with the main group.

Overall, anxiety and depression scores were higher in patients with epilepsy compared with the control group, confirming the clinical relevance of affective disorders in epilepsy.

In the main group, the mean HADS-A score was 9.24 ± 1.23 (n = 46), indicating mild anxiety symptoms in most patients. In the comparison group, the mean HADS-A score was 9.43 ± 1.17 (n = 37), showing a similar level of anxiety severity.

Spearman correlation analysis showed a very weak negative correlation between disease duration and HADS-A score ($r = -0.10$; $p = 0.533$), which was not statistically significant. No significant correlation was found between seizure frequency during the last 6 months and HADS-A score ($r = -0.03$; $p = 0.841$). In the comparison group, a strong negative correlation was observed between disease duration and seizure frequency ($r = -0.65$; $p < 0.001$), whereas anxiety level was not significantly associated with either disease duration ($r = 0.02$; $p = 0.903$) or seizure frequency ($r = -0.07$; $p = 0.673$).

Analysis of depressive symptoms showed no significant correlation between HADS-D score and disease duration ($r = -0.04$; $p = 0.774$) or seizure frequency ($r = 0.06$; $p = 0.687$) in the main group. Similar results were observed in the comparison group, where HADS-D score was not significantly associated with disease duration ($r = 0.01$; $p = 0.962$) or seizure frequency ($r = 0.10$; $p = 0.563$). However, a strong negative correlation between disease duration and seizure frequency was found ($r = -0.65$; $p < 0.001$), suggesting a tendency toward reduced seizure frequency with longer disease course.

Further analysis evaluated plasma NGF levels in the main, comparison, and control groups and their association with cognitive function (MoCA) and depressive symptoms (HADS-D). NGF levels differed significantly between the groups (e.g. Table 3.1).

Table 3.1. Distribution of NGF levels in the study groups expressed percentages and mean values

	Group	Number of patients	%	Mean ± Std.
NGF pg/ml	Comparison	37	35,58%	33,6 ± 17,06
	Main1c	27	25,96%	22,78 ± 7,02
	Control	15	14,42%	28,28 ± 4,54
	Main 1b	12	11,54%	19,41 ± 3,59
	Main 1a	7	6,73%	13,01 ± 1,7

Table 3.1 compares plasma NGF (pg/ml) levels in the main, comparison, and control groups and their subgroups. The analysis showed that NGF levels differed between the groups and demonstrated considerable variability.

The highest mean NGF level was observed in the comparison group (33.6 ± 17.06 pg/ml), which was higher than in the control group and may indicate relatively increased neurotrophic activity in this group.

In the control group, the NGF level was 28.28 ± 4.54 pg/ml (n = 15) and showed lower variability compared with the patient groups, suggesting relatively stable NGF levels in healthy individuals.

In the subgroups of the main group, a gradual decrease in NGF levels was observed. The mean NGF level was 22.78 ± 7.02 pg/ml in subgroup main 1c, 19.41 ± 3.59 pg/ml in subgroup main 1b, and 13.01 ±1.70 pg/ml in subgroup main 1a. This trend suggests that lower NGF levels may be associated with greater clinical severity of epilepsy and more pronounced cognitive or emotional impairment in the main group (Figure 3.3).

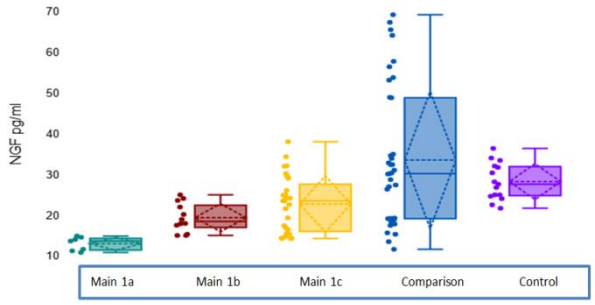

Figure 3.3. Plasma NGF levels (pg/ml) across study groups. Error bars represent standard deviation

Changes in NGF levels according to disease duration in the main and comparison groups with different etiologies are presented in Figure 3.4.

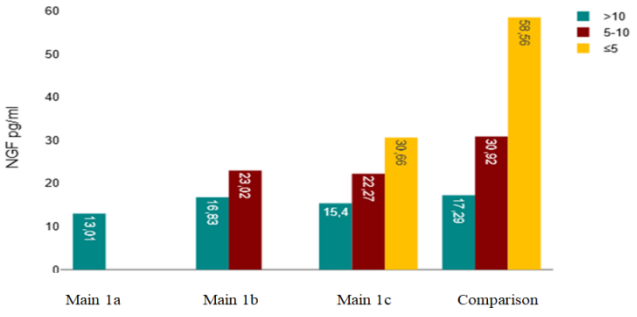

Figure 3.4. Changes in NGF levels according to disease duration in the study groups

A clear gradational change in NGF levels was observed depending on disease duration. In all groups, the highest NGF levels were found in patients with shorter disease duration (≤5 years), intermediate values in those with 5–10 years, and the lowest levels in patients with epilepsy lasting more than 10 years.

In the subgroups of the main group, NGF levels decreased progressively with increasing disease duration. The lowest NGF values were observed in patients with duration >10 years (e.g., 13.01 pg/ml in main 1a), whereas values of approximately 22–23 pg/ml were found in the 5–10 year group and up to 30.66 pg/ml in patients with duration ≤5 years. This trend suggests gradual depletion of neurotrophic resources during chronic epileptic activity.

In the comparison group, NGF levels were higher than in the main group at all stages of disease duration, particularly in patients with ≤5 years of epilepsy, where NGF reached 58.56 pg/ml. In the 5–10 year group, NGF was 30.92 pg/ml, and in patients with duration >10 years it decreased to 17.29 pg/ml. A similar decline in NGF levels with longer disease duration was also observed in this group, indicating a general reduction of neurotrophic activity in long-standing epilepsy regardless of etiology.

In the control group, NGF levels were approximately 28.28 pg/ml, which was close to the values observed in patients with early-stage epilepsy (≤5 years).

The visual trends corresponded to a strong negative correlation between NGF level and disease duration ($r = -0.76$; $p < 0.001$), confirmed by mixed-model ANOVA, indicating that the decrease in NGF depended both on time and group characteristics.

Figure 3.5 shows changes in NGF levels according to annual seizure frequency in different clinical groups. Seizure frequency was categorized as 0, 1–2, 3–12, and ≥12 per year.

One-way ANOVA showed significant differences in NGF levels between groups ($p < 0.05$).

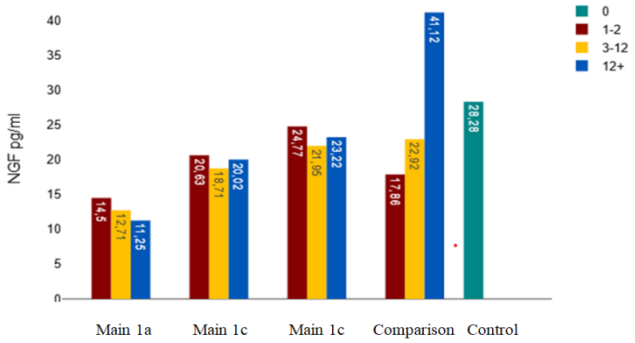

Figure 3.5. Changes in plasma NGF levels according to annual seizure frequency in the study groups

Spearman correlation analysis revealed a moderate positive correlation between NGF level (pg/ml) and cognitive performance assessed by MoCA in the main group. The correlation was statistically significant ($r = 0.39$; $n = 44$; $p = 0.007$) (e.g. Figure 3.6).

In the comparison group, Spearman correlation analysis showed a very weak positive correlation between baseline MoCA scores and plasma NGF level (pg/ml), which was not statistically significant ($r = 0.02$; $p = 0.884$).

To evaluate the relationship between NGF level and affective symptoms, correlation analysis was performed between NGF concentration and HADS-A and HADS-D scores.

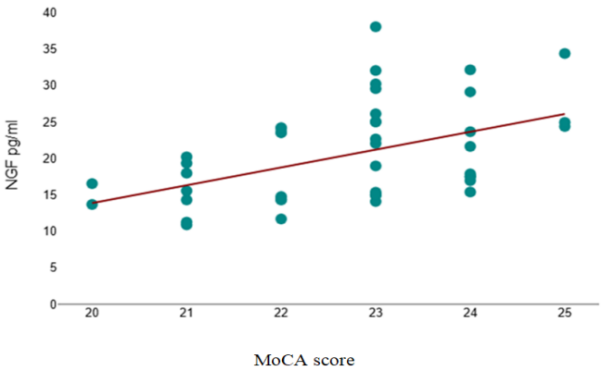

Figure 3.6. Relationship between plasma NGF level and MoCA score in the main group

In the main group, a weak positive correlation was found between NGF level and HADS-A score, but it was not statistically significant ($r = 0.21$; $p = 0.161$). Similarly, in the comparison group, the correlation between NGF level and HADS-A score was very weak and not significant ($r = 0.01$; $p = 0.942$).

Analysis of depressive symptoms showed a weak positive correlation between NGF level and HADS-D score in the main group ($r = 0.29$), which did not reach statistical significance ($p = 0.054$), although the result approached the level of significance. This finding suggests a possible association between NGF and affective disturbances, but the evidence was insufficient to confirm a reliable relationship.

In the comparison group, a weak positive correlation was also observed between NGF level and HADS-D score ($r = 0.10$; $p = 0.541$), which was not statistically significant, indicating that plasma NGF level was not directly associated with the severity of depressive symptoms.

Overall, in both the main and comparison groups, correlations between NGF level and affective symptoms (HADS-A and HADS-D) were weak and mostly not significant. Only in the main group was a trend toward a positive association between NGF level and depression observed ($p \approx 0.05$). These results suggest that NGF may be involved in the pathogenesis of affective disorders, but it cannot be considered a reliable independent biomarker based on the present data.

4. Discussion

In this study, the relationship between cognitive function, affective status, and plasma nerve growth factor (NGF) levels was evaluated in patients with generalized epilepsy. The results showed that certain clinical characteristics of epilepsy, particularly disease duration and seizure frequency, were associated with cognitive decline. In the main group, longer disease duration was associated with lower cognitive performance. The negative correlation between MoCA scores and disease duration suggests that long-standing epilepsy may lead to progressive functional changes in the central nervous system. In addition, the negative association between seizure frequency and cognitive function indicates that recurrent epileptic activity may contribute to a reduction in cognitive reserve. These findings are consistent with previous studies reporting that repeated epileptic discharges and neuronal network reorganization may play an important role in the development of cognitive impairment.

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Analysis of psychoemotional status demonstrated higher levels of anxiety and depression in patients with epilepsy compared with the control group. However, no significant correlations were found between HADS scores and clinical parameters such as disease duration or seizure frequency, suggesting that affective disturbances may also be influenced by psychosocial factors and individual adaptive mechanisms.

An important part of the study was the evaluation of plasma NGF levels in different groups. The results showed a tendency toward decreased NGF levels with longer disease duration. Neurotrophic factors, including NGF, play a key role in neuronal survival, synaptic plasticity, and maintenance of neural connections; therefore, reduced NGF levels may reflect weakening of neurotrophic mechanisms during chronic epileptic activity.

A moderate positive correlation between NGF level and cognitive performance in the main group suggests that NGF may act as a biological factor supporting cognitive function. Higher NGF levels were associated with better cognitive scores, which may reflect the role of neurotrophic factors in maintaining neuronal plasticity. In contrast, no statistically significant relationship was found between NGF level and affective symptoms.

These findings are consistent with previous studies demonstrating the role of neurotrophic factors in epilepsy and cognitive impairment (Iughetti et al., 2018). Previous studies have mainly focused on BDNF as a key neurotrophic factor in epilepsy (Iughetti et al., 2018). However, the role of NGF remains insufficiently studied. Our results suggest that NGF may also contribute to cognitive impairment in generalized epilepsy.

This study has several limitations, including a relatively small sample size and single-time measurement of NGF levels. In addition, the potential effect of antiepileptic drugs on NGF concentration was not analyzed separately. Nevertheless,

the findings suggest that NGF may be a biological factor associated with cognitive impairment in generalized epilepsy and indicate the need for further research in this area.

5. Conclusions

In the main group, a statistically significant negative correlation was found between disease duration and cognitive performance ($p = 0.023$), and a moderate negative correlation was observed between seizure frequency and MoCA scores ($p = 0.002$), while no significant associations between these variables were detected in the comparison group. Analysis of psychoemotional status showed that anxiety levels were highest in subgroup comparison 2b and lowest in subgroup main 1a, whereas depressive symptoms were subclinically higher in subgroup comparison 2a. However, no statistically significant correlations were found between HADS-A or HADS-D scores and disease duration or seizure frequency. Plasma NGF levels were higher in the comparison group and demonstrated a strong negative correlation with disease duration ($p < 0.001$), while the relationship between NGF level and seizure frequency was non-linear. In the main group, a moderate positive and statistically significant correlation was found between NGF level and cognitive performance ($p = 0.007$), whereas correlations between NGF level and anxiety or depression scores were weak and not statistically significant.

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