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The Role of Amphiregulin and Epidermal Growth Factor Receptor in First-Episode Psychosis: Exploring Links to Schizophrenia Pathophysiology

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ABSTRACT

Introduction: Despite these efforts, the pathogenesis of schizophrenia remains unclear. Recent studies suggest that excessive synaptic pruning during adolescence may contribute to schizophrenia, potentially linking it to uncontrolled apoptosis. Given its role in inflammation and apoptosis, amphiregulin may play a key role in this process. The objective of this study was to investigate the role of the Amphiregulin/Epidermal Growth Factor Receptor (EGFR) complex in the pathogenesis of schizophrenia.

Methods: Seventy-three drug-naive patients who were admitted to our outpatient clinic or hospitalized in our clinic and diagnosed for the first time with a psychotic disorder spectrum according to Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), along with 77 healthy controls matched for sociodemographic characteristics and who did not have a history of psychiatric or chronic diseases were recruited for the study. The patients' symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), administered by a skilled psychiatrist. Blood samples were collected from all participants to measure amphiregulin and EGFR levels.

Results: A statistically significant positive correlation was found between amphiregulin and EGFR levels in the patient group. However, there was no significant difference in serum amphiregulin and EGFR levels between the first-episode psychosis group and the healthy control group. Additionally, a positive correlation was observed between both age and age of onset of the disease and serum EGFR levels in the patient group, a correlation that was not present in the healthy control group.

Conclusion: The similar correlation between amphiregulin and its receptor in the central nervous system suggests that amphiregulin levels may play a stable role in the disease process rather than being a primary driver of disease development. It remains unclear whether plasma neurotrophins accurately reflect central neurotrophic activity. The presence of amphiregulin in serum, which is thought to be secreted by regulatory T cells (Tregs) in the central nervous system, may be low. Further studies using cerebrospinal fluid and brain tissue samples are particularly needed in schizophrenia research.

Keywords: Amphiregulin, biomarker, epidermal growth factor receptor, first episode psychosis, neurotrophic factor, synaptic pruning

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INTRODUCTION

Schizophrenia is a chronic and progressive mental disorder that affects approximately 1% of the global population, with onset typically occurring in early adulthood (1). Several hypotheses have been proposed to gain a deeper understanding of the pathogenesis of this complex disease, including the stress-diathesis, neurodevelopment, neurodegeneration, and neurotransmitter-related hypotheses involving dopamine and glutamate (2). Recent studies have highlighted the critical role of synaptic pruning, predominantly occurring during adolescence, in the pathogenesis of schizophrenia (3). It is possible that uncontrolled synaptic pruning is associated with uncontrolled apoptotic processes. While it is established that microglia are key mediators of atypical apoptosis, the precise mechanisms through which they exert this effect remain unclear

Highlights

- **Amphiregulin may not be prominent in disease development.**
- **EGFR levels increase with age, possibly linked to higher reactive astrogliosis.**
- **Further studies on cerebrospinal fluid and brain tissue are needed in schizophrenia.**

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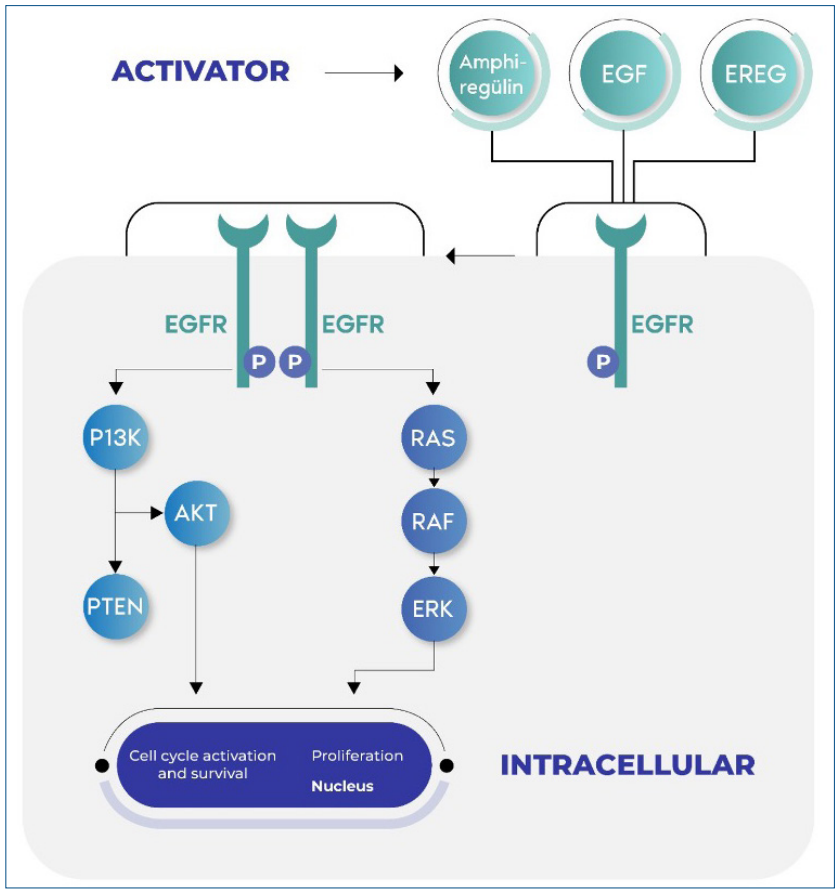

Figure 1. EGFR activation and signalling pathway. Binding of a specific ligand triggers autophosphorylation of the receptor's tyrosine kinase domain. This activation leads to the activation of signalling pathways such as Ras/Raf/MEK/ERK, PI3K/AKT/mTOR, PLC_{γ}/PKC, and CaMK and Src/STAT 3/5. These pathways culminate in the activation of transcription factors that induce various biological responses.

(4). Recent research has focused on neurotrophic and apoptotic factors to explain this process, suggesting that uncontrolled apoptosis may result from an imbalance between these factors.

Numerous studies have shown that brain-derived neurotrophic factor, nerve growth factor, and neuregulin-1 –neuropeptides involved in neuroplasticity, neural migration, and neurogenesis– are significantly reduced in schizophrenia (5,6). In recent years, the neurotrophic effects of amphiregulin, which has been extensively studied in cancer metabolism due to its role in anti-apoptotic processes, have gained increasing attention in the literature. Amphiregulin is expressed in the adult brain, particularly in the ventricular system, choroid plexus, and hippocampus, where it regulates neural stem cell proliferation and neurogenesis (7).

Studies on the central nervous system are crucial for understanding the role of amphiregulin. Ito et al. demonstrated that, following ischemic stroke, regulatory T cells (Tregs) accumulate in the brain and contribute to neurological recovery. Treg-derived amphiregulin suppresses astrogliosis by inhibiting the IL-6-STAT3 signaling pathway. In amphiregulin-deficient Treg mice, intraventricular administration of amphiregulin reduced neurotoxic astrocyte gene expression, astrogliosis, and neuronal apoptosis (8). Amphiregulin produced by Tregs suppresses excessive astrocyte-mediated immune responses. In schizophrenia, reduced amphiregulin expression may lead to astrocyte overactivation, contributing to neuroinflammatory processes, synaptic dysfunction, and neurotransmitter imbalances (9).

Epidermal growth factor receptor (EGFR), also known as ErbB1 or HER-1, is one of the earliest described members of a structurally related family of tyrosine kinase receptors known to play crucial roles in oligodendrogenesis, myelination, neurogenesis and synaptogenesis (10). Epidermal growth factor receptor activation and signaling pathway is summarized in Fig. 1. Animal studies suggest that acute or sub-chronic activation of EGFR in the brain can cause dopamine release in the striatum or globus pallidus, resulting in behavioural abnormalities associated with schizophrenia (11). In contrast to their actions on dopaminergic neurons, some EGFR ligands can inhibit the growth of Gamma-aminobutyric acid-releasing neurons in the prefrontal cortex and decrease the activation of glutamate receptor channels in these neurons (12).

The present study aimed to elucidate the involvement of the Amphiregulin/EGFR complex in the pathogenesis of schizophrenia. We hypothesized that amphiregulin levels would be lower in patients compared to the control group, while EGFR levels would be higher in patients.

METHODS

Selection Criteria for Patients and Controls

This study includes 80 drug-naive patients who were diagnosed for the first time with a disorder within the schizophrenia spectrum and other psychotic disorders, according to Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. These patients were recruited from outpatient clinics affiliated with Prof. Dr. Mazhar Osman Bakırköy Mental and Nervous Diseases Training and Research Hospital and were monitored by an experienced psychiatrist over a period of four to six weeks. Seven patients were excluded from the analysis: one patient due to a positive urine metabolite test, and six patients because their diagnoses were revised during follow-up. The revised diagnoses included two cases of mental retardation, one case of depression with psychotic features, and three cases of bipolar mood disorder. Additionally, a control group of 77 healthy individuals was selected to match the patients in terms of age, gender, and marital status. These individuals had no prior

psychiatric history and were found to have no psychiatric disorders in the psychiatric interview before being included in the study. The control group participants were drawn from individuals attending the polyclinic for administrative procedures or from hospital staff undergoing routine occupational health and safety evaluations.

Exclusion criteria were applied to both groups, which included being younger than 18 or older than 47 years, fewer than eight years of education, the presence of intellectual disability, having sensory impairments (e.g., vision or hearing deficits) that could impede communication, or a diagnosis of systemic or neurological diseases such as hypertension, diabetes mellitus, infections, dementia, epilepsy, Parkinson's disease, cardiovascular, renal, urological, hepatic diseases, or any other conditions likely to confound study outcomes. Individuals with pulmonary, genetic, or endocrine disorders, nutritional deficiencies, a body mass index (BMI) outside the range of 18.0–25.0, recent intoxication, or a history of surgery or other organic disorders were also excluded. Further exclusion criteria included the use of non-psychiatric medications, a family history of psychiatric disorders, head trauma within the past year, or a history of regular alcohol or substance abuse within the preceding six months. Patients with first-episode psychosis (FEP) who exhibited comorbid psychiatric disorders were also excluded. To ensure the absence of recent substance use, urine screening tests were conducted for all participants.

Ethical Approval

Ethical approval was obtained prior to the commencement of the study. Each participant was provided with an informed consent form, which detailed the research specifics. Only the participants who consented to volunteer were permitted to sign this form. All participants provided written informed consent. The study was conducted in accordance with the ethical standards of the Ethical Committee of Dr. Sadi Konuk Training and Research Hospital (IRB Date/Number: 18.01.2021/02). The present study was financially supported by the Health Sciences University Türkiye Research Projects Unit (Date/Number: 08.11.2021/149).

Data Collection Tools

Sociodemographic and clinical data form

The forms comprised a series of questions pertaining to sociodemographic variables, including age, gender, educational attainment, marital status, and income level. Moreover, they incorporated clinical parameters, including illness duration, height, and weight. The aforementioned forms were administered to both the patient and control groups for completion.

Positive and negative syndrome scale (PANSS)

The PANSS was employed for the assessment of the severity of the illness in patients diagnosed with FEP. The scale was developed by Kay et al. and consists of 30 items, each of which is rated on a 7-point severity scale. The instrument is organised into three primary subdomains. Seven items are used to measure positive symptoms, seven to assess negative symptoms, and the remaining 16 to evaluate general psychopathology (13).

Blood sample collection

After an overnight fast, venous blood samples (5 mL) were drawn into coagulant tubes containing gel between 07:00 and 09:00 a. m. The samples were allowed to clot at room temperature for two hours, followed by centrifugation at 3000 rpm for 20 minutes at 4°C to separate the serum. The resulting serum was divided into 0.5 mL aliquots and stored at -80°C until further analysis.

Protein assays

The serum levels of EGFR and amphiregulin were quantified using commercially available kits based on enzyme-linked immunosorbent assay (ELISA) technology [EGFR: (E-EL-H0060; Lot No: XIFIA9IVA9, Human EGFR Elisa Kit, Elabscience, USA), Amphiregulin: (E-EL-H0237; Lot No: ALTTREJL97, Human AR Elisa Kit, Elabscience, USA)]. The assays were carried out according to the manufacturer's instructions using an automatic ELISA system (Allsheng, China). To minimize assay variability, protein concentrations for all subjects were assessed on the same day. The intra-assay coefficient of variation (CV) for each measurement was below 10%, and the inter-assay CV was similarly under 10%. No notable cross-reactivity or interference was detected during the assays.

Statistical analysis

The statistical analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) program version 22 (IBM, Türkiye). The Shapiro Wilk test was employed to ascertain whether the study parameters exhibited a normal distribution. In the evaluation of the study data, descriptive statistical methods (mean, standard deviation, and frequency) were utilized. For the comparison of quantitative variables, the Kruskal-Wallis test was employed to compare groups when the parameters did not show a normal distribution. The Student's t-test was employed to ascertain whether parameters distributed normally between two groups exhibited significant differences, whereas the Mann-Whitney U test was utilised to determine whether non-normally distributed parameters between two groups demonstrated notable discrepancies. A Chi-square test, together with a Continuity (Yates) Correction, was employed for the purpose of comparing qualitative data. The relationships between parameters with a normal distribution were analysed using Pearson's correlation coefficient. The level of significance was set at $p < 0.05$.

RESULTS

Descriptive variables

Table 1 presents a comparison of the socio-demographic characteristics of the groups included in the study. Our study included a total of 150 participants, 60 (40%) women and 90 (60%) men. The study examined two groups: 73 (48.7%) FEP patients and 77 (51.3%) HC. Evaluation of sociodemographic data indicated no difference in the gender ratio, age, BMI, and educational level (p=0.689, p=0.832, p=0.159, p=0.561, respectively) between the two groups. However, the HC group had significantly higher rates of marriage and employment compared to the FEP patient group (p=0.014 and; p<0.05, respectively). The mean PANSS total score of the FEP group was 119.58±12.78.

Table 1 provides a comparison of the biochemical parameter between FEP patients and HC. The mean amphiregulin level was 129.41±92.12 in the patient group and 132.2±91.8 in the control group (p=0.870). The mean EGFR level was 2.2±2.08 in the patient group, and 2.52±2.7 in the control group (p=0.998). No significant difference in the levels of amphiregulin or EGFR could be identified between the two groups.

Correlation of biochemical values, PANSS and age of disease onset in FEP patients

Our study identified a statistically significant positive correlation between amphiregulin and EGFR levels in the patient group (r=0.302, p=0.009). However, no significant correlation was observed between PANSS scores and variables such as the age at onset of disease, amphiregulin levels, or EGFR levels in the patient group (p >0.05) (Table 2). Similarly, no significant correlation was found between the age at onset and amphiregulin levels in the patient group (p >0.05) (Table 2).

In the healthy control (HC) group, EGFR levels did not correlate significantly with age (r=-0.084, p=0.47). In contrast, in the patient group, a significant positive correlation was observed between age and EGFR levels (r=0.356, p=0.002) as well as between age at onset and EGFR levels (r=0.358, p=0.002) (Table 2). The relationship between age at onset and serum EGFR levels is further illustrated in Fig. 2.

Table 1. Comparison of sociodemographic and clinical data and biochemical values of patients with FEP and healthy controls (mean ± sd)

		Patients with FEP (n=73)	Healthy Controls (n=77)	p
Age in years (median)		29.63±7.59	29.9±8.26	[1]**0.838**
Gender	Female Male	28 (38%.4) 45 (61%.6)	32 (41%.6) 45 (58%.4)	[2]**0.689**
BMI (median)		23.34±4.85	24.34±3.63	[1]**0.159**
Education Level (years)	<12 years >12 years	22 (30%.2) 51 (69%.9)	18 (23%.4) 59 (76%.7)	[2]**0.561**
Smoking history	No Yes	39 (53%.4) 34 (46%.6)	31 (40%.3) 46 (59%.7)	[2]**0.16**
Marital status	Married Other	20 (27%.4) 53 (72%.6)	36 (46%.8) 41 (53%.2)	[2]**0.01***
Occupational Status	Unemployed Employed	60 (82%.2) 13 (17%.8)	18 (23%.4) 59 (76%.6)	[3]**0.001***
Disease onset age (min-max; mean ± SD)	Female Male	14–44; 28.00±8.02 17–45; 27.98±7.39		
Amphiregulin (pg/mL) (mean ± SD)		129.41±92.12	132.2±91.8	[4]**0.870**
EGFR (ng/mL) (mean ± SD)		2.2±2.08	2.52±2.7	[4]**0.998**

*p<0.05; [1]Student t test; [2]Chi-square test; [3]Yates' correction were used for statistical analyses; [4]Mann-Whitney U test was used for statistical analyses; BMI: body mass index; EGFR: epidermal growth factor; FEP: first episode psychosis.

Table 2. Correlation of between biochemical, PANSS scores and disease onset age in patients with FEP

	PANSS General	PANSS Positive	PANSS Negative	PANSS Total	Disease onset age	Age (FEP)	AREG (FEP)	EGFR (FEP)	AREG (HC)	EGFR (HC)	Age (HC)
PANSS General	1										
PANSS Positive	0.67**	1									
PANSS Negative	0.77**	0.37**	1								
PANSS Total	0.90**	0.40**	0.51**	1							
Disease onset age	0.014	-0.024	-0.202	-0.119	1						
Age (FEP)	-0.047	0.022	0.217	0.159	0.926**	1					
AREG (FEP)	-0.085	0.13	0.075	0.08	-0.081	0.05	1				
EGFR (FEP)	-0.078	0.018	-0.024	-0.043	0.358*	0.356**	0.302**	1			
AREG (HC)									1		
EGFR (HC)									0.192	1	
Age (HC)									0.054	-0.084	1

*p<0.05, Pearson correlation analysis was performed; **p<0.01, Spearman correlation analyses was performed; AREG: amphiregulin, EGFR: epidermal growth factor; FEP: first episode psychosis; HC: healthy control; PANSS: positive and negative syndrome scale.

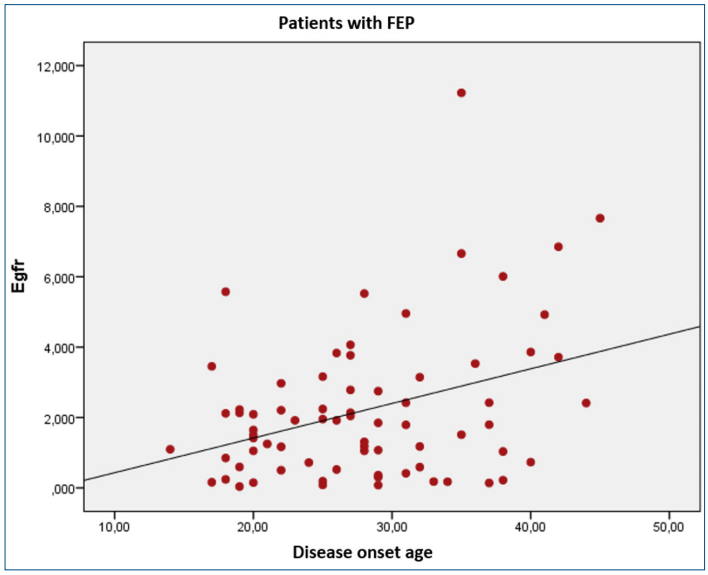

Figure 2. Evaluation of the correlation between disease onset age and EGFR in patients with FEP.

DISCUSSION

This is the first study to investigate the potential involvement of the amphiregulin/EGFR complex – previously hypothesised to be of significant importance – in the pathogenesis of schizophrenia. A thorough review of existing literature on schizophrenia pathogenesis suggests that excessive synaptic pruning, which primarily occurs during adolescence and early adulthood, may play a crucial role in the development of the disorder. Neuroimaging studies of individuals with schizophrenia have revealed a greater reduction in gray matter volume than would be expected based on the normal physiological process of synaptic pruning. Additionally, recent studies have indicated that microglial activation and elevated levels of C3 and C4 complement proteins may contribute to severe synaptic pruning in schizophrenia patients by promoting neuronal cell apoptosis through enhanced macrophage-apoptotic cell interactions (14). Furthermore, it is widely accepted that inflammatory cells play a pivotal role in the process of apoptosis (15). It may be hypothesised that the hyperactivation of apoptotic signalling pathways could result in excessive synaptic pruning, particularly in instances where amphiregulin, a protein involved in both apoptotic and inflammatory processes, is produced in insufficient quantities in individuals with schizophrenia.

The present study did not reveal any significant differences in serum amphiregulin levels between the FEP patients and the HC group. Amphiregulin is known to be secreted at a high rate from the placenta, plays a vital role in the development and proliferation of neurons, and contributes to brain development during the prenatal period (16). It may be thought that this protein, which has been shown to be especially active in the neurodevelopmental process, is not sufficiently active in the synaptic pruning process or that its antiapoptatic property, which is especially prominent in peripheral tissues, is not sufficiently effective on the nervous system.

However, this hypothesis has yet to be supported by clinical findings and does not provide comprehensive predictions regarding how various environmental factors influence the risk of psychosis. Adversities experienced during childhood, along with current stressors, pose risks for numerous mental disorders and may modulate the development of the CNS and immune systems. Furthermore, it remains unclear whether any circulating effects persist in the context of constitutional Treg hypofunction in meningeal or intracerebral h-Tregs. The extent to which plasma neurotrophins truly reflect central neurotrophic activity is another source of variability. In our study, serum amphiregulin levels did not show a significant difference between the patient group and the healthy control group. It's possible that the serum's reflection of amphiregulin, which is believed to be released by Tregs in the CNS, was low. This is why more research involving CSF and brain tissue is required, particularly in cases of schizophrenia.

The receptor ligand interaction between Amphiregulin and EGFR can play a fundamental role in the neural development process. Epidermal growth factor receptor (ErbB1) is a member of the ErbB receptor family and can be activated by seven different ligands. Previous studies have suggested that the ErbB receptor family may be a key regulator of dopamine-dependent oligodendrogenesis, accounting for myelination disorders observed in schizophrenia (17). Liu et al. demonstrated that astrocytes expressed significantly elevated levels of EGFR in response to injury-related reactive astrogliosis (18). Reactive astrogliosis was reported in 70% of schizophrenia patients in regions such as the thalamus and the limbic system (19). Animal studies suggest that EGFR signalling may be implicated in both positive and negative symptoms seen in schizophrenia patients (20). In addition, postmortem studies with schizophrenia patients have directly revealed elevated EGFR expression in the brain tissue of schizophrenic patients (21). We did not observe any significant difference in serum EGFR levels between the patient and control groups. This may be because amphiregulin is not the only ligand for EGFR. Thus, the activity and levels of other proteins that stimulate EGFR may contribute towards the regulation of its expression. Therefore, additional studies are required to evaluate all proteins that act on EGFR. In addition, the study revealing high EGFR levels in the brain tissue of schizophrenic patients had only six patients in the drug-free schizophrenia group (21). The current study was carried out with drug naive FEP patients. The relationship between antipsychotic use and EGFR levels is unknown; thus, future studies are needed to examine EGFR levels in schizophrenia patients receiving antipsychotic treatment. Studies have shown that gliosis in the rostral and caudal regions was more prevalent in patients with late-onset schizophrenia (22). Recent studies suggest that the differences in EGFR levels can be explained by the differences in patient age (23). In support of this difference, no significant correlation was found between EGFR and age in the healthy control group, whereas a positive correlation was found between both age and age at disease onset and EGFR serum levels in the patient group. We speculate that EGFR levels rise with increasing age, potentially due to an increase in reactive astrogliosis.

An analysis of the correlation between amphiregulin and EGFR levels in the patient and control groups separately revealed a statistically significant positive correlation between amphiregulin and EGFR levels in the patient group, in contrast to the control group. This suggests that the balance between amphiregulin and its receptor may be specifically maintained to prevent pathogenesis in the initial stages of the disease. This may also have precluded any significant difference in the Amphiregulin/EGFR ratio between the FEP and the HC groups.

The current study has some limitations. Although all participants were free of infection at the time of sampling, the lack of cytokine and infective biomarker analysis, in addition to Amphiregulin/EGFR levels, represents a limitation. Moreover, our findings were not supported by methods like postmortem tissue sampling, which could be considered another limitation.

As a result the results of our study demonstrated a statistically significant positive correlation between amphiregulin and EGFR levels in the patient group. However, no significant difference was observed in serum amphiregulin and EGFR levels between the FEP and HC groups. The positive correlation between the expression of amphiregulin and its receptor in the CNS suggests that amphiregulin may play a stabilising role in disease development and is not a primary factor in disease progression. No significant correlation was found between EGFR and age in the healthy control group, whereas a positive correlation was found between both age and age at disease onset and EGFR serum levels in the patient group. This suggests that EGFR levels increase with increasing age due to increased reactive astrogliosis. Due to the heterogeneity of the neurobiological basis of schizophrenia spectrum disorder, additional research is required to determine the role of Amphiregulin/EGFR levels in the pathogenesis of schizophrenia disease, particularly in CSF samples containing a combination of neurotrophic factors.

Ethics Committee Approval: The study was conducted in accordance with the ethical standards of the Ethical Committee of Dr. Sadi Konuk Training and Research Hospital (IRB Date/Number: 18.01.2021/02).

Informed Consent: All participants provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- BGT, ÜHY, NK; Design- BGT, ÜHY, NK; Supervision- BGT; Resource- BGT; Materials- BGT; Data Collection and/or Processing- BGT; Analysis and/or Interpretation- BGT, ÜHY, ZÇ; Literature Search- BGT; Writing- BGT, ÜHY; Critical Reviews- NK.

Conflict of Interest: The authors declared that there is no conflict of interest.

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