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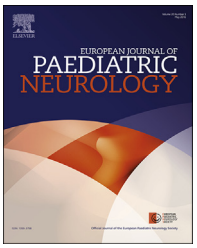

Original Article

Increased insulin-like growth factor-1 levels in cerebrospinal fluid of advanced subacute sclerosing panencephalitis patients

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ABSTRACT

Purpose: Subacute sclerosing panencephalitis (SSPE) is a progressive, lethal disease. Brain histopathology in certain SSPE patients shows, neurofibrillary tangles composed of abnormally phosphorylated, microtubule-associated protein tau (PHF-tau). Because the, phosphorylation of tau is inhibited by insulin and insulin-like growth factor-1 (IGF-1), we investigated cerebrospinal fluid (CSF) insulin and IGF-1 levels in SSPE patients.

Methods and Results: In this study CSF IGF-1 and insulin levels of 45 SSPE and 25 age-matched control patients were investigated. CSF IGF-1 levels were significantly higher in SSPE patients at stage 4, compared to other stages (p 0.05). CSF insulin and IGF-1 levels were both positively correlated with serum measles IgG.

Conclusions: The correlation between CSF insulin and IGF-1 levels and serum measles virus IgG titer may be the result of, insulin activating IGF-1 receptors, and consequently, IGF-1 stimulating, plasma cells and enhancing IgG production. Increased IGF-1 may also, inhibit the phosphorylation of tau. Further studies examining the, correlation between IGF-1, insulin, tau, and PHF-tau levels in the same, patients may clarify any possible pathogenetic relation between these, pathways.

1. Introduction

Subacute sclerosing panencephalitis (SSPE) is a slow central nervous system (CNS) infection caused by measles virus. Histopathologically it is characterized by neuronal loss, atrophy of gray and white matter, inflammatory infiltration and demyelination. Neurofibrillary tangles have been reported in about 20% of patients with SSPE.[1,2] They are composed mainly of abnormally phosphorylated microtubule-associated

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protein tau (PHF-tau).[3] Tau stabilizes microtubule structures. However, hyperphosphorylated tau leads to neurofibrillary tangle formation and neuronal degeneration.[3] The phosphorylation of tau is inhibited by apolipoprotein E, insulin and insulin-like growth factor-1 (IGF-1). Insulin and IGF-1 are members of the tyrosine kinase receptor family whose signaling pathways control vital brain functions such as survival, growth, energy metabolism, neuroprotection and neuroregeneration.[4–7] Disturbance in insulin or IGF-1 signaling pathways are reported to increase tau phosphorylation.[8,9] The aim of this study is to investigate cerebrospinal fluid (CSF) insulin and IGF-1 levels for their possible role in SSPE.

2. Patients and methods

Forty-five patients diagnosed with SSPE in Hacettepe University Ihsan Dogramaci Children's Hospital and Dr Sami Ulus Children's Hospital between January 2004 and August 2008 were included in the study. The diagnosis was made according to clinical features and elevated CSF measles antibody titers.[1] Lumbar puncture was done at initial presentation for diagnostic purposes, before any treatment. One or 2 cc CSF was obtained and stored at −20 °C. Neurological disability of the patients was evaluated according to SSPE Scoring System (SSS) where higher scores indicate worsening of neurological deficit.[1] Clinical staging was done as described previously: stage 1 includes mental and behavioral changes, stage 2: myoclonic spasms and ambulation with/without support, stage 3: bedridden, may have some myoclonic spasms, and stage 4: no myoclonic spasms, neurovegetative stage.[10,11] History of clinical measles infection and immunization, period between first symptoms and diagnosis, latent period between measles infection and initial symptom of SSPE, presence of myoclonia, EEG findings including the frequency of periodical discharges, and brain magnetic resonance imaging (MRI) features were recorded.

The age- and sex-matched control group (n = 25) consisted of patients who underwent lumbar puncture for various reasons: patients with leukemia or lymphoma in whom CNS involvement was excluded and no intrathecal treatment had been administered in the last 6 months (n = 13), patients with idiopathic increased intracranial pressure (n = 5), intractable epilepsy (n = 2) and others (brachial plexopathy, Behçet's disease, chronic inflammatory demyelinating neuropathy, mental deterioration of unknown etiology and fever of unknown etiology, n = 1 each).

The study was approved by a research ethics committee and informed consent was obtained from all patients or parents.

Cerebrospinal fluid samples were immediately centrifuged at 1500 rpm, treated with acetic acid for solid phase extraction and stored at −20 °C for up to 2 months until assay. Insulin and IGF-I levels were measured using immunoradiometric assay (IRMA, Immunotech, Marseilles, France) according to manufacturer's instructions.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Continuous variables were tested for normal distribution using Shapiro–Wilk test. Continuous data were shown as mean ± SD or median (minimum–maximum), and nominal data were presented as number and percentage of cases. Means of the patient and control groups were compared using Student's t test and Mann Whitney U test depending on whether the distribution of continuous variables did or did not conform to normal distribution. Differences between stages of the disease were evaluated comparing median values by the Kruskal–Wallis test. When the p value from the Kruskal–Wallis test statistics was significant, multiple comparisons test was used to discern the groups causing the difference. The degree of association between continuous variables was calculated by Spearman's "rho"correlation coefficient. Nominal data analysis was performed by Pearson Chi-square test. $p < 0.05$ was considered statistically significant.

3. Results

Forty-five SSPE (13 female, 32 male) and 25 control (7 female, 18 male) patients were studied. Median ages of the SSPE and control patients were 8^{2-15} years and 7^{2-15} years, respectively. Age and sex distribution were similar in SSPE and control groups. Mean age of measles infection was 18.4 ± 14.1 months. The clinical features are shown in Table 1. Stages of SSPE patients were: Stage 1, n = 19 (42.2%), Stage 2, n = 15 (33.3%), Stage 3, n = 8 (17.8%) and Stage 4, n = 3 (6.7%). Patients who were already at stages 3 and 4 when admitted had presented late to the referring center, or had been referred after initial investigations in regional hospital. Myoclonia were observed in 30 patients (66.7%). Measles IgG titers were not significantly different among stages (Table 2). The frequency of generalized periodic slow wave complexes on EEG was ≤5 per minute in 27 patients and ≥6 per minute in 16 patients, while two patients had no such discharges. Thirty-four patients had a cranial MRI at the time of diagnosis: 58.8% were normal, 14.7% had white matter involvement and 26.5% both white and gray matter involvement.

The median concentration of CSF IGF-1 was 26.00 ng/ml in SSPE and 17.07 ng/ml in control patients ($p > 0.05$). CSF IGF-1 levels were significantly higher in stage 4 patients in the SSPE group compared to other stages ($p < 0.05$) (Table 3 and Fig. 1).

Median CSF insulin levels were 1.28 uIU/ml in SSPE and 1.11 uIU/ml in control patients ($p > 0.05$). CSF insulin levels were similar in patients at various stages of SSPE ($p = 0.651$) (Table 3) and when early stages (stages 1 and 2) were compared with late stages (stages 3 and 4).

Table 1 – Clinical features of the SSPE group.

	Minimum	Maximum	Mean ± SD	Median
Interval measles-SSPE (months)	18	144	66.9 ± 31.8	57
Duration of symptoms (months)	1	220	16.6 ± 43.9	4
SSS score[a]	4	52	15.8 ± 11.4	12

[a] Scoring system reflecting severity of symptoms and signs of SSPE.[1]

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