Epilepsy Research (2011) 95, 184—187

journal homepage: www.elsevier.com/locate/epilepsyres

SHORT COMMUNICATION

The serum level of interleukin-6 in patients with intellectual disability and refractory epilepsy

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Received 24 November 2010; received in revised form 7 February 2011; accepted 5 March 2011
Available online 29 April 2011

KEYWORDS
Cytokine;
Epilepsy;
Interleukin-6;
Seizure frequency;
Intellectual disability

Summary We aimed to study the influences of active epilepsy and intellectual disability (ID) on the serum interleukin-6 (IL-6) by determining levels in 74 patients with developmental disorder with epilepsy and 63 healthy controls. The patients showed significantly higher IL-6 levels than the controls (4.1 ± 4.5 pg/ml vs. 2.1 ± 1.0 pg/ml; $p < 0.001$). High seizure frequency and severe intellectual disability emerged as predictors for elevated serum levels of IL-6.

Introduction

Several studies suggest that interleukin-6 (IL-6) is involved in the pathogenesis of neuropsychiatric disorders. So far, we know that elevated serum IL-6 is a predictor for abnormal outcome in neonatal encephalopathy (Ramaswamy et al., 2009). Further, elevated serum IL-6 levels have been reported in children with Down syndrome (DS) (Corsi et al., 2006) and in demented adults with Down syndrome (Kálmán et al., 1997). IL-6 levels have been measured in patients with autism spectrum disorders (Vargas et al., 2005; Li et al., 2009) as well as in patients with fragile-X syndrome suggesting the cytokine profile to be altered in these conditions (Ashwood et al., 2010, 2011). In a group of patients with intellectual disability (ID), Carmeli et al. found that those with epilepsy represented higher IL-6 levels than those without epilepsy (Carmeli et al., 2009). Elevated IL-6 levels have been reported in epilepsy both in post-ictal (Peltola et al., 2000; Bauer et al., 2009) and interictal states (Hulkkonen et al., 2004; Nowak et al., 2010).

The present study focused on patients with ID and active epilepsy. The objective was to ascertain whether specific etiological entities, specific epilepsy syndromes, as well as the patients' seizure frequency, severity of cognitive impairment, medication, chronological age, and onset age of epilepsy influence serum levels of IL-6.

Materials and methods

Inclusion criteria for present study were ID and at least a five-year history of refractory epilepsy. Blood samples were obtained in connection to other laboratory investigations in order to determinate serum IL-6 levels. Healthy blood donors served as controls. Com-

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doi:10.1016/j.eplepsyres.2011.03.004

Table 1 Etiological groups and specific diagnoses of the 74 study patients.

Etiological groups	Diagnosis
Genetic syndromes (15)	Down syndrome (4), X-linked mental retardation (2), trisomy 15q (2), Angelman (1), deletion 6q (1), autosomal dominant familial disorder (2), Kabuki (1), unidentified dysmorphic syndrome (2)
Genetic diseases (7)	Aspartylglucosaminuria (2), spinocerebellar ataxia (1), neurofibromatosis type 2 (1), MELAS (1), x-linked familial (1), Dravet (1)
Cortical dysgenesias (15)	Polymicrogyria (6), temporal dysmyelination (4), microcephalia (2), schizenkefalia (1), pachygyria (1), lissenencephalia (1)
Acquired encephalopathias (31)	Post-asphyxial (11), post-infectious (8), mesial temporal sclerosis (5), early severe epilepsy (4) and post-traumatic (3)
Unknown etiology, genetic and/or acquired conditions (6)	Infantile autism (4), unspecific intellectual disability with generalized epilepsy (2)

mercially available assay was used to determine serum IL-6 levels (Pelikine Compact, CLB, The Netherlands). As statistical methods we used independent samples *t*-test and one-way ANOVA to compare IL-6 levels between groups. Pearson correlation test was used to calculate correlations between numeric variables and chi square test was used in comparison of group differences between study groups. SPSS version 17.0 was used in statistical analysis. A p value of 0.05 or less was considered statistically significant. The ethical committee of Tampere University Hospital approved the study design.

Results

Clinical data

The study group comprised 74 patients (age range 15—61, mean age 35 years) and 63 controls (age range 16—65 years, mean age 36 years). All patients had undergone a detailed analysis of their condition including video-EEG, brain MRI as well as consultation with a clinical geneticist and psychologist. The patients' etiological diagnoses in detail are presented in Table 1 and other clinical data in Table 2. Sixty-four patients (86%) had experienced first seizures during childhood or adolescence. Brain MRI of 12 patients (eight with an acquired encephalopathia and four with a genetic disorder) disclosed hippocampal sclerosis. All patients except one were on polytherapy. Fifty-five patients received valproate, 28 topiramate, 25 lamotrigine, 16 oxcarbatsepine, 10 levetirasetame, 9 carbamazepine, 9 clobatsame, 8 clonazepam, 7 vigabatrine, 6 gabapentine, 5 phenytoin, 2 ethosuximide, 2 azetatsolamide, and 2 phenobarbitale.

Serum IL-6 levels

The patients showed significantly higher serum IL-6 levels than the controls (4.1 ± 4.5 vs. 2.1 ± 1.0; $p < 0.001$). Table 2 displays the serum IL-6 levels separately according to seizure frequencies, epilepsy syndromes, etiological diagnoses and severity of ID. High seizure frequency correlated with elevated IL-6 levels whereas the patients with yearly only 1—11 seizures did not differ from controls. Among these patients with normal IL-6 and rare seizures were the three of the five with an idiopathic generalized epilepsy (of them two with genetically unconfirmed generalized epilepsy with febrile seizures plus, one with juvenile absence epilepsy, and two with atypical myoclonic-astatic epilepsy), two of the six with unknown etiology as well as six of the 13 with mild to moderate level of ID (Table 2). IL-6 levels were significantly elevated in patients with severe to profound but not in patients with mild to moderate ID compared to controls (Table 2). Patients with an epileptic encephalopathy ($n = 30$) had the highest mean seizure frequencies and showed quite equally elevated IL-6 levels. Of these 30 patients, 17 had profound ID. Of the etiological subgroups the highest IL-6 levels were detected among patients with Down syndrome ($n = 4$; mean 6.3 ± 1.6 pg/ml; one with yearly and three with weekly seizures) and X-linked mental retardation ($n = 2$; 13.6 and 19.4 pg/ml; one with monthly and one with weekly seizures). The four patients with infantile autism showed on average slightly lower IL-6 (3.2 ± 1.2 pg/ml) than other subgroups; they all had monthly seizures. Neither chronological age of the patient, onset age of epilepsy, nor medications correlated to IL-6 levels.

Discussion

Our study results are convergent with existing data on high seizure frequency and severe intellectual disability being risk factors for an elevated serum IL-6. Other predictors may be Down and X-linked ID syndromes comorbid with epilepsy. Seizure frequencies were highest among patients with an epileptic encephalopathy, which all showed quite equally elevated IL-6 levels. We found no earlier theme related studies on epileptic encephalopathia other than West syndrome and thus consider our results as novel and preliminary.

In previous studies we have reported transiently elevated plasma IL-6 levels within few hours after the seizure and proposed that this cytokine release may be caused by neuronal excitation (Lehtimäki et al., 2004). However, present study revealed elevated IL-6 levels also in patients with weekly to monthly seizures. Thus, it is unlikely that elevation in IL-6 is fully explained by post-ictal increase but maybe reflect chronic inflammatory system activation resulting from recurrent seizures. So far, many publications on cytokine and epilepsy concentrate on localization related epilepsy (Hulkkonen et al., 2004; Bauer et al., 2009; Alapirtti et al., 2009; Liimatainen et al., 2009). The results of the three last mentioned papers indicate that temporal lobe epilepsy is more likely to affect IL-6 basal than extra-