Available online at www.sciencedirect.com
SCIENCE DIRECT®
Epilepsy & Behavior 6 (2005) 191–195
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Serum IgA, IgG, and IgM concentrations in patients with epilepsy and matched controls: a cohort-based cross-sectional study

Jouni Ranua[a,*], Katja Luoma[b], Anssi Auvinen[c], Jukka Peltola[d], Anna-Maija Haapala[e], Jani Raitanen[c], Jouko Isojärvi[b]

[a] Department of Neurology, Seinäjoki Central Hospital, Hanneksenrinne 7, Seinäjoki, FIN-60220, Finland
[b] Department of Neurology, University of Oulu, P.O. Box 5000, Oulu, FIN-90014, Finland
[c] School of Public Health, University of Tampere, Tampere, FIN-33014, Finland
[d] Department of Neurology, Tampere University Hospital, Tampere, FIN-33521, Finland
[e] Department of Clinical Microbiology, Tampere University Hospital, Tampere, FIN-33521, Finland

Received 29 September 2004; revised 29 November 2004; accepted 29 November 2004

Abstract

Conflicting reports have been published on serum immunoglobulin (Ig) concentrations in patients with epilepsy. Serum IgA, IgG, and IgM concentrations were determined in a cohort of 958 patients and in a reference population of 581 subjects. Overall, 8.2% of patients with epilepsy and 1.9% of control subjects had low serum IgA concentrations. Low serum IgA levels were measured in 19.1% of patients currently on phenytoin therapy and in 11.9% of patients who had previously been treated with phenytoin, whereas only 3.8% of patients who had never been on phenytoin therapy had low serum IgA. In multivariate analysis low serum IgA concentrations were associated with phenytoin medication and female gender. No differences in serum IgG and IgM concentrations were observed between patients and control subjects. However, in patients with epilepsy, low serum IgG concentrations were associated with concomitant autoimmune diseases, and low IgM levels with older age at the onset of epilepsy, long duration of epilepsy, and autoimmune diseases. In conclusion, the prevalence of low serum IgA concentrations was increased in patients with epilepsy, but serum IgG and IgM concentrations were similar in patients with epilepsy and reference subjects. The low serum IgA concentrations were associated with phenytoin medication. In addition to current phenytoin medication, previous phenytoin therapy also was associated with low serum IgA concentrations. This implies that phenytoin medication may have permanent immunological effects in some patients.

Keywords: Immunoglobulin A; Immunoglobulin G; Immunoglobulin M; Epilepsy; Autoimmune diseases; Autoantibodies; Antiepileptic medication

1. Introduction

Epilepsy is a multifactorial paroxysmal brain disorder in which both environmental and genetic factors are implicated. Involvement of the immune system has been suggested to contribute to the pathogenesis of some forms of epilepsy. Recent studies on antibodies against GluR3 peptides in Rasmussen's encephalitis and severe intractable seizures [1] and previous results of immunological treatments in catastrophic childhood epilepsies [2] have increased interest in the immunological attributes of epilepsy. An increased presence of antiphospholipid and antinuclear antibodies has been reported in both adult and pediatric patients with epilepsy [3–5], but in a recent report on a large unselected adult epilepsy population, their presence was the same as in a reference population [6]. However, long duration of epilepsy and poor seizure control were associated with an increased presence of antiphospholipid

* Corresponding author. Fax: +358 6 4154297.
E-mail address: jouni.ranua@netikka.fi (J. Ranua).

1525-5050/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2004.11.017

antibodies in patients with epilepsy in that study, too [6]. High glutamate acid decarboxylase antibody titers have been reported in patients with epilepsy as well [7].

Changes in serum immunoglobulin (Ig) concentrations in patients with epilepsy have been reported since the 1970s. Decreased IgA levels and IgA deficiency have been described most commonly [8,9], but reports conflict [10]. Changes in IgA levels have been reported, especially with phenytoin treatment [11,12]. Phenytoin has been associated with changes in both humoral and cellular immunity [12,13], development of lupus erythematosus [12], and anticonvulsant hypersensitivity syndrome [14]. Carbamazepine has also been implicated in changes in humoral and cellular immunity [12,13,15,16]. However, reports on serum IgG and IgM levels as well as IgG subgroups in patients with epilepsy have been more contradictory [17–19]. The clinical significance of the reported changes in serum Ig concentrations in patients with epilepsy is debatable. However, increased susceptibility to respiratory infections has been postulated [8,9]. Genetic predisposition has been suggested to explain the reported changes in serum Ig concentrations [9].

We studied serum IgA, IgG, and IgM concentrations in a cohort of 958 patients with epilepsy and 581 reference subjects from the general population matched for age, gender, and municipality of residence to determine the effects of medication, type and duration of epilepsy, number of seizures, age, age at the onset of epilepsy, sex, and comorbidity on serum Ig levels.

2. Methods

2.1. Study subjects

The study was conducted at the Outpatient Department of Neurology, Oulu University Hospital, with the approval of the Ethics Committee of the Medical Faculty of University of Oulu. Oulu University Hospital is the primary referral center for all adult patients with epilepsy from a source adult population of approximately 260,000. The target population consisted of 1386 patients treated for epilepsy at Oulu University Hospital during the years 1996–1997. The patient population represents a comprehensive prevalence sample of adult patients treated for epilepsy in the community. All patients were asked to participate in the study. In all, 958 patients gave their informed consent and took part in the study. The patient population consisted of 491 male subjects (51.3%) and 467 female subjects (48.7%). The mean ± SD age of the patients was 46.4 ± 15.7 years. The mean ± SD age at the onset of epilepsy was 28.4 ± 19.0 years, and the mean ± SD duration of epilepsy 15.2 ± 11.9 years. Eight hundred and thirty-three patients (87.0%) had partial epilepsy, 90 patients (9.4%) primary generalized epilepsy, and 35 patients (3.6%) unclassified epilepsy. Blood samples were drawn and patient charts were reviewed retrospectively to obtain all pertinent medical information. Serum Ig concentrations for each patient were determined from a single sample.

The type of epilepsy was classified according to the recommendations of the International League Against Epilepsy [20]. Among the patients, 51.0% were seizure-free, 31.4% had fewer than one seizure per month, 9.4% had one to three seizures per month, and 8.2% had four or more seizures per month. The most commonly used antiepileptic drugs (as mono- or polytherapy) were carbamazepine (48.4%), oxcarbazepine (27.5%), valproate (20.1%), lamotrigine (10.4%), and phenytoin (9.0%).

In addition, 1386 reference subjects matched for age, gender, and municipality of residence were identified from the Finnish Population Registry and were asked to participate in the study. Five hundred eighty-one reference subjects agreed to participate. The reference population consisted of 252 male subjects (43.4%) and 329 female subjects (56.6%). The mean age of the reference population was 47.2 ± 14.4 years. Blood samples were obtained after receiving informed consent.

2.2. Measurements

The laboratory analyses were performed at the Centre for Laboratory Medicine, Tampere. Immunoglobulins were measured by a routine nephelometric method using the Behring BN II analyzer. The cutoff values from the manufacturer were used. Normal ranges are 0.88–4.84 g/L in men and 0.52–4.02 g/L in women for IgA, 6.77–15 g/L in both men and women for IgG, and 0.36–2.59 g/L in men and 0.47–2.84 g/L in women for IgM. Values below these ranges were deemed low, those within the limits normal, and those above the ranges high. Subjects with IgA serum concentrations below 0.06 g/L were deemed IgA deficient.

2.3. Statistical methods

A generalized linear model with a binomial error structure and logarithmic link function was used to estimate the prevalence ratio, i.e., relate prevalence of decreased immunoglobulin levels in patients with epilepsy to those in the reference group. Gender, age at observation, and comorbidity were regarded as potential confounders and adjusted by multivariate modeling. Statistical significance was evaluated by two-sided likelihood ratio tests.

3. Results

Serum concentrations of immunoglobulins are listed in Table 1.