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Post-ictal circulating levels of allopregnanolone in children with partial or generalized seizures

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Abstract

Introduction: Allopregnanolone (3α-hydroxy-5α-pregnan-20-one) is a neurosteroid with a potent modulating activity on the gamma-aminobutyric acid $(GABA)_A$ receptor complex. It plays a key role in the epileptogenesis of partial seizures. Serum allopregnanolone concentrations significantly increase in the postcritical phase. In the present study we investigated the post-ictal serum allopregnanolone levels in children with partial seizures and generalized seizures, respectively.

Patients and methods: Three groups of subjects were included in the study. Group 1 consisted of 18 children affected by complex partial seizures. Group 2 consisted of 11 children presenting with generalized epilepsy. Group 3 consisted of 20 healthy age-matched subjects. Serum allopregnanolone levels were assayed in the inter-ictal phase and within 30 min after an epileptic event.

Results: The data we obtained suggest that circulating allopregnanolone level significantly increases in the post-ictal phase. However, we found no significant differences in the post-ictal serum allopregnanolone concentrations between patients with partial seizures and those with generalized seizures.

Conclusions: Further studies are needed to establish if allopregnanolone is a reliable circulating marker of epileptic seizures. However, our observations seem to indicate that post-ictal circulating allopregnanolone level is not useful in differentiating focal and generalized epilepsy events.

Keywords: Allopregnanolone; Neurosteroids; Epilepsy; Partial seizures; Generalized seizures

1. Introduction

Allopregnanolone (3α-hydroxy-5α-pregnan-20-one) derives from progesterone and belongs to the so-called neurosteroids, a group of steroid hormones

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synthesized in the brain (Mellon and Vaudry, 2001). Important peripheral sources of allopregnanolone are represented by adrenal glands and ovaries (Genazzani et al., 1998). As allopregnanolone is the most potent endogenous neurosteroid know to modulate the gamma-aminobutyric acid $(GABA)_A$ receptor complex (GRC) (Belelli et al., 1990; Frye, 1995; Frye and Scalise, 2000; Lambert et al., 1995). It may be involved in several CNS processes (Grobin et al., 2003; Galderisi et al., 2003; Ghoumari et al., 2003) and exerts a significant neuroprotective effect after traumatic brain injuries (Djebaili et al., 2004). Allopregnanolone is also involved in the pathogenesis of epilepsy (Belelli et al., 1989; Frye, 1995). In this perspective, a number of experimental data showed that allopregnanolone is an important protector against seizures in a wide range of models (Czlonkowska et al., 2000; Finn et al., 1995; Kaminski et al., 2003; Maciejak et al., 2002; Salazar et al., 2003). In particular, allopregnanolone is clearly involved in the epileptogenesis of partial seizures (Beyenburg et al., 2000). Previous studies have demonstrated that in humans, serum allopregnanolone levels increase after epileptic seizures, indicating that the neurosteroid might be considered as a possible serum marker of an epileptic event (Galli et al., 2001; Grosso et al., 2003). However, no investigations have been performed to evaluate whether there exist differences in the post-ictal circulating allopregnanolone levels, between patients with partial seizures and those with generalized seizures.

1.1. Patients and methods

The patients were recruited from our clinic and selected according to the following criteria: (i) aged less than 8 years or at pubertal Tanner's stage I; and (ii) suffering from well defined type of epilepsy with partial or generalized seizures. Exclusion criteria were the presence of: (i) neurological progressive disorder, and (iii) neuro-endocrine dysfunction. Patients who underwent ACTH/corticosteroids treatment were also excluded from the study. Family and personal histories were registered and neurological examinations performed on all the patients. Electroencephalograms (EEGs) were recorded during wakefulness, spontaneous sleep and arousal, with hyperventilation, and with photic stimulation in those subjects with sufficient collaboration. Long-term video EEGs were performed when considered useful to classify the type of epilepsy. All patients underwent imaging studies with brain magnetic resonance imaging (MRI). Biochemical analyses, chromosomal investigations, and screening for metabolic disorders were carried out in all patients. Seizures were classified in accordance with the International League against Epilepsy (ILAE) classification of epileptic seizures (Commission, 1981). Patients with mixed type of seizures, or with secondary generalization were excluded from the study.

1.1.1. Subjects

Three groups of subjects were included in the study (Table 1). Group 1 consisted of 18 patients (8 girls and 10 boys, aged 2.0–9.4 years) affected by complex partial seizures (CPS). Group 2 consisted of 11 patients (5 girls and 6 boys, aged 1.3–10 years) presenting with generalized epilepsy. Three patients Group 3 consisted of healthy children ($n = 20$, 8 girls and 12 boys, age range between 1.8 and 8.2 years) coming in for annual check-up at the Department of Pediatrics of the University of Siena. No one of these children had suffered from epilepsy or other neurologic disorders. Informed consent for blood withdrawal was obtained from the parents of all groups of patients.

1.1.2. Inter-ictal blood specimens

All subjects of the three groups were submitted to a blood withdrawal in the morning. Epilepsy patients must have been seizure-free from at least 12 h before blood withdrawal.

Post-ictal blood specimens. In all patients of groups 1 and 2, blood samples were drawn immediately, within 30 min after the patient's seizures. Patients were seizure free from at least 6 h after the recorded attack. Each seizure attack was accepted as epileptic only if it had been witnessed by a reliable observer (doctors or members of the nursing staff). Semeiology of each seizures were reported on a patient's schedule. Clinical features of the patients are summarized in Table 1. In 18 patients clinical and EEG features were congruent with a diagnosis of CPS. In six CPS were correlated to the temporal lobe, in another seven to an extra-temporal focus. In five patients, although clinical findings were congruent with diagnosis of CPS, the correlation with a specific lobe was impossible. In another 11 patients electroclinical findings were congruent with a gener-