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Original article

Investigation of neuronal auto-antibodies in children diagnosed with epileptic encephalopathy of unknown cause

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Abstract

Aim: Cryptogenic forms of epileptic encephalopathies (EE) with their well-known features of drug-resistance, mental deterioration and partial response to immunotherapies are ideal candidates for screening for neuronal autoantibodies (NAA).

Method: Fifty consecutive pediatric patients with a diagnosis of EE of unknown cause were included. Nine NAAs were tested by ELISA, RIA or cell-based assays. Clinical features of seronegative and seropositive patients were compared.

Results: NAAs were found in 7/50 (14%) patients. They were N-methyl-D-aspartate receptor in two (4%), glycine receptor in two (4%), contactin-associated protein-like 2 in one (2%), glutamic acid decarboxylase in one (2%) and type A gamma aminobutyric acid receptor in one patient (2%). Furthermore, serum IgGs of two patients negative for well-characterized NAAs, showed strong reactivity with the uncharacterized membrane antigens of live hippocampal neurons. There were no significant differences between seropositive and seronegative patients by means of epilepsy duration, anti-epileptic drug resistance, EE type, types of seizures, seizure frequencies, EEG features or coexisting autoimmune diseases. Some seropositive patients gave good-moderate response to immunotherapy.

Discussion: Potential clues for the possible role of autoimmunity in seropositive patients with EE were atypical prognosis of the classical EE type, atypical progression and unusual neurological findings like dyskinesia.

Keywords: Epileptic encephalopathy; Neuronal auto-antibodies; West syndrome; Lennox-Gastaut syndrome; Immune-mediated epilepsy

1. Introduction

As an exciting development in recent years, various neuronal auto-antibodies (NAA) were detected in many patients with autoimmune encephalitis often associated with drug-resistant epilepsy and status epilepticus [1]. Seizures associated with NAA are divided into two main clinical groups in adults and children [2,3]. While in adults, these antibodies mostly cause epileptic syndromes that are associated with temporal lobe inflammation, in children, they are often associated with autoimmune encephalopathies that present with diffuse involvement of the brain [4]. The most commonly described antibodies are those directed against the voltage gated potassium channel (VGKC)-complex and its subtypes, glutamic acid decarboxylase (GAD) and N-methyl-D-aspartate receptor (NMDAR) [5].

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Epileptic encephalopathies (EE) are mysterious electroclinical conditions where cognitive and neurological functions deteriorate due to enormous epileptic activity and are mostly seen in infancy and early childhood [6]. Various etiological factors (developmental brain anomalies, metabolic, genetic and acquired lesions) have been demonstrated in a minority of the patients, while disease mechanisms of EE remain unclear in most of the patients [6]. West syndrome (WS) with epileptic spasms usually responding to adrenocorticotrophic hormone (ACTH) treatment and its follower in age spectrum, Lennox-Gastaut syndrome (LGS) presenting with many types of drug-resistant seizures are among the most frequently observed EEs. Some of these patients may also show propensity to respond to other immune treatment options such as intravenous immunoglobulin (IVIg); thus they could be considered as ideal candidates for "autoimmune epilepsy" [7]. Furthermore, WS patients have been shown to demonstrate dysfunction in cellular immunity, changes in Ig levels, and T lymphocyte dysfunction further supporting the autoimmunity hypothesis [8]. Moreover, in a recent case report with epileptic spasms, VGKC-complex antibodies were shown in association with status epilepticus [9]. There are currently no reports on the systematic screening of a cryptogenic EE cohort for the presence of various NAA except patients with acute onset febrile infection related epilepsy syndrome [10].

Possible new treatment modalities at least in a subgroup of EEs are of utmost importance for these patients. In this study, we aimed to investigate the frequency of the NAAs in a cohort of patients diagnosed with EE of unknown origin and to identify their clinical characteristics.

2. Methods

2.1. Material/Subjects

We included 50 consecutive patients, (female/male: 18/32; mean age: 10.84 (±8.89); range: 1–36 years; mean duration of epilepsy 9.34 ± 8.9 years, range 1–35 years) who were followed in Istanbul Faculty of Medicine, Department of Child Neurology unit between the years of 2012 and 2014 and had been diagnosed as EE with their typical clinical and EEG findings according to the ILAE criteria [11]. EE was defined as the cognitive, sensory or motor deterioration due to prominent epileptic activity as suggested and patients were grouped as WS, LGS and other/undetermined EE. Age and gender-matched 40 healthy volunteers were also enrolled as the control group. For each investigated antibody, sera of 4–5 autoimmune encephalitis or paraneoplastic syndrome patients that were previously found seropositive were used as positive control. Data regarding demographics such as age, gender, neurological symptoms, age at onset, epilepsy duration, seizure types, presence of febrile seizures, medical and family history, history of autoimmune disorders, medication at the time of serum sampling, response to treatment and detailed EEG and neuro-imaging findings were collected from the files. Their prognosis was categorized according to the Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS) and Communication Function Classification System (CFCS9) [12]. According to these classification system scores, patients were divided into four groups as good (normal motor and mental status or mild mental retardation), moderate (moderate motor and mental retardation), bad (severe motor and mental retardation) and exitus. To assess the cognitive status, Denver or Alexander tests were used depending on the age of the subjects. Response to immunotherapy was also divided into three groups as good response (≥50% seizure decline when compared to basal monthly seizure frequency), moderate (20–50% seizure decline) and no response (<20% seizure decline). Drug-resistant epilepsy was defined according to the ILAE commission proposal [13].

All patients underwent a detailed neurological evaluation with clinical examination, seizure history and routine EEG with scalp electrodes (32 channels, non-invasive EEG monitoring with 10–20 system electrodes and ECG electrodes). EEG investigations were reviewed by the first two authors to ensure the correct diagnoses. Background activity, epileptiform interictal and ictal patterns and specific EEG patterns such as extreme delta brush were also listed according to a standardized form. Moreover, all patients underwent magnetic resonance imaging (MRI) examinations with 1.5 T scanners with a standard epilepsy protocol and were evaluated by an experienced neuroradiology team. Seizures and syndromes were diagnosed according to the revised terminology, and concepts for organization of seizures and epilepsies of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology [11]. The syndrome diagnosis of EE of unknown cause was supported by the EEG and neuropsychological tests, besides evaluation of biochemistry and MRI to identify symptomatic causes.

In an effort to exclude symptomatic causes of EE, brain MRI was supplemented with a detailed routine investigation scheme, including investigations of biotidinase deficiency, pyridoxine deficiency, mitochondrial disorders, glycosylation defects, phenylketonuria and other aminoaciduria, TORCH infections and peroxisomal and lysosomal disorders for differential diagnosis. Patients with tuberous sclerosis were also excluded. Moreover known genetic causes of EE were investigated and found negative in all participants.

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