Journal of Neuroimmunology 293 (2016) 34–38

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Prevalence of antineuronal antibodies in patients with encephalopathy of unknown etiology: Data from a nationwide registry in Korea

Jung-Ick Byun [a,b,1], Soon-Tae Lee [a,b,1], Keun-Hwa Jung [a,b], Jun-Sang Sunwoo [a,b], Jangsup Moon [a,b,c], Tae-Joon Kim [a,b], Jung-Ah Lim [a,b], Soyun Kim [a], Do-Yong Kim [a], Su-Hyun Han [d], Hyemin Jang [e], Hong Il Suh [f], A-Hyun Cho [g], Dong Wook Kim [h], Jung-Won Shin [i], Yong Seo Koo [j], Woo Chan Choi [k], Woong-Woo Lee [l], Nari Choi [m], Seongheon Kim [n], Hyunwoo Nam [o], Dae Lim Koo [o], Minah Kim [p], Byung Chan Lim [q], Jong-Hee Chae [q], Ki Joong Kim [q], Daejong Jeon [a], Kyung-Il Park [a,r], Ki-Young Jung [a,b], Manho Kim [a,b,s], Kon Chu [a,b,*], Sang Kun Lee [a,b,*]

[a] Department of Neurology, Laboratory of Neurotherapeutics, Seoul National University Hospital, Seoul, South Korea
[b] Program in Neuroscience, Seoul National University College of Medicine, Seoul, South Korea
[c] Departments of Neurology, Ewha Womans University School of Medicine and Ewha Medical Research Institute, Seoul, South Korea
[d] Department of Neurology, Asan Medical Center, Seoul, South Korea
[e] Department of Neurology, Samsung Medical Center, Seoul, South Korea
[f] Department of Neurology, Ajou University Medical Center, Suwon, South Korea
[g] Department of Neurology, Catholic University of Korea Yeouido St. Mary's Hospital, Seoul, South Korea
[h] Department of Neurology, Konkuk University, Seoul, South Korea
[i] Department of Neurology, CHA University, CHA Bundang Medical Center, Seongnam, South Korea
[j] Department of Neurology, Korea University Anam Hospital, Seoul, South Korea
[k] Kyungpook National University School of Medicine, Daegu, South Korea
[l] Department of Neurology, Eulji General Hospital, Seoul, South Korea
[m] Department of Neurology, Soonchun Hyang University Hospital Cheonan, Cheonan, South Korea
[n] Department of Neurology, Kangwon National University Hospital, Chuncheon, South Korea
[o] Department of Neurology, Seoul Metropolitan Government–Seoul National University Boramae Medical Center, Seoul, South Korea
[p] Department of Psychiatry, Seoul National University Hospital, Seoul, South Korea
[q] Department of Pediatrics, Seoul National University Children's Hospital, Seoul, South Korea
[r] Department of Neurology, Seoul National University Hospital Healthcare System Gangnam Center, South Korea
[s] Protein Metabolism Research Center, Seoul National University College of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 1 February 2016
Accepted 5 February 2016

Keywords:
Autoimmune
Encephalopathy
Autoimmune synaptic antibody
Classic paraneoplastic antibody
Prevalence

ABSTRACT

We aimed to evaluate the prevalence of antineuronal antibodies in a nationwide cohort of patients with encephalopathy of unknown etiology. We screened 1699 patients with idiopathic encephalopathy who were referred from 70 hospitals across Korea for autoimmune synaptic and classic paraneoplastic antibodies. Those with cerebellar degeneration, sensory polyneuropathy or other paraneoplastic syndromes without encephalopathy were not included in this study. One-hundred and four patients (6.12%) had antibody-associated autoimmune encephalopathy. Autoimmune synaptic antibodies were identified in 89 patients (5.24%) and classic paraneoplastic antibodies were identified in 16 patients (0.94%). The patients with antibody-associated autoimmune encephalopathy comprised a small but significant portion of the total number of patients with encephalopathy of unknown cause.

1. Introduction

Antibody-associated autoimmune encephalopathy is an emerging disease category that causes focal or diffuse neuronal dysfunction (Leypoldt et al., 2015). It commonly involves limbic structures and presents as cognitive impairment, seizures, and psychiatric symptoms (Dalmau and Rosenfeld, 2008). The antibodies may target synaptic proteins (autoimmune synaptic antibodies, ASAbs), such as N-methyl-

* Corresponding authors at: Department of Neurology, Seoul National University Hospital, 101, Daehak-Ro Jongno-Gu, Seoul 03080, South Korea.
E-mail addresses: stemcell.snu@gmail.com (K. Chu), sangkun2923@gmail.com (S.K. Lee).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jneuroim.2016.02.002
0165-5728/

D-aspartic acid or N-methyl-D-aspartate (NMDA) receptors; leucine-rich, glioma inactivated 1 (LGI1); Caspr2; gamma-aminobutyric acid-b (GABAb) receptors; and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA1) receptors (Lancaster et al., 2011; Irani et al., 2014; Linnoila et al., 2014). Alternatively, the antibodies may target intracellular proteins (classic paraneoplastic antibodies), such as Hu, Ma2/Ta, amphiphysin, Ri, and CV2/CRMP5 (Graus et al., 2004; Dalmau and Rosenfeld, 2008). The detection of the antibodies strongly supports the diagnosis of autoimmune encephalopathy and provides a rationale for immunotherapy, which offers the best chance for clinical improvement (Zuliani et al., 2012). However, extent of the contribution of the antibodies in patients with idiopathic encephalopathy is unknown. Moreover, the relative frequency of the individual antibodies associated with the encephalopathy is unclear.

Due to the rarity and complexity of the disease, extensive epidemiological and clinical studies of antibody-associated autoimmune encephalopathy are lacking. Only a few epidemiologic studies have reported the incidence of antibodies in patients with encephalitis. In a population-based study of 203 encephalitis patients in England, anti-NMDAR and anti-VGKC antibodies were detected in 4% and 3% of the patients, respectively (Granerod et al., 2010). A single center study of 198 acute encephalitis patients identified anti-NMDAR and anti-VGKC antibodies in 5.4% of the patients (Singh et al., 2015). However, the focus of these studies was not to evaluate the prevalence of autoantibodies but to identify the possible etiology of encephalitis; thus, only limited antibody types were evaluated. Less is known about the prevalence of other autoimmune synaptic or classic paraneoplastic antibody-related encephalopathy.

In this study, we prospectively enrolled a nationwide sample of a large number of patients with encephalopathy of unknown etiology and tested their serum or cerebrospinal fluid (CSF) for both autoimmune synaptic and classic paraneoplastic antibodies. We evaluated the prevalence of the autoimmune encephalopathy and the associated antibody types along with their clinical characteristics and underlying neoplasms.

2. Methods

From January 2013, we conducted a prospective, nationwide, multicenter registry of autoimmune encephalitis in Korea named KASPER (Korea Autoimmune Synaptic and Paraneoplastic Encephalitis Registry). Consecutive patients with encephalopathy of undetermined etiology who visited Seoul National University Hospital (SNUH), or whose samples were sent there, were included in the registry. Because SNUH is the only center that performs this type of antibody testing in Korea (population of 50,965,180 as of Jan. 2013), physicians send patient's serum or CSF samples to SNUH for antibody testing when autoimmune encephalopathy is suspected. Those with cerebellar degeneration, sensory polyneuropathy or other paraneoplastic syndromes without encephalopathy were not included in this study.

We tested the serum or CSF for both autoimmune synaptic and classic paraneoplastic antibodies as described previously (Shin et al., 2013). In brief, the presence of the antibodies was initially screened by immunostaining rat brain sections with patients' serum (1:100) and CSF (1:10). Then, we tested all samples for the presence of ASAbs (anti-NMDAR, -LGI1, -Caspr2, -AMPA1, -AMPA2, and -GABAb-R antibodies) using cell-based immunocytochemistry (Euroimmune Ag, Germany), and for the presence of classic paraneoplastic antibodies (anti-Hu, -Yo, -Ri, -Ma2, -amphiphysin, and -CV2/CRMP5 antibodies) via indirect immunofluorescence testing using immunoblotting. The clinical characteristics of the patient at the time of admission as well as the results of initial diagnostic tests, including brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and CSF evaluation, were obtained from questionnaires filled out by the study investigators or the referring physicians. This study was approved by the Institutional Review Board of Seoul National University Hospital. Written informed consent to participate was obtained from the enrolled patients or their next-of-kin.

The case definition of this study included patients of any age with positive serum or CSF results for either autoimmune synaptic or classic paraneoplastic antibodies. For each patient, the following information was reviewed: autoantibody type; clinical symptoms (cognitive impairment, psychiatric symptoms, seizure, movement disorder, and decreased level of consciousness); the results of brain MRI, EEG and CSF evaluation; and the type of underlying neoplasm. Patients with an alternative final diagnosis were excluded from the analysis. CSF leukocytosis was defined as a CSF WBC count $>5/mm^3$, and CSF protein elevation was defined as a CSF protein level >35 mg/dL. Neoplasm screening was conducted by either chest and abdomen computed tomography or whole-body fluorodeoxyglucose positron emission tomography. Only neoplasm that was diagnosed within 5 years of the development of symptoms was included (Dalmau and Rosenfeld, 2008).

2.1. Statistical analysis

The patients were grouped into four groups according to antibody type: classic paraneoplastic, anti-NMDA receptor, anti-LGI1, and other ASAbs. Because the number of patients in the other ASAb group was too small to achieve statistical significance, they were not included in the analysis. The patients were categorized into 9 decade-based age groups (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80–89 years). Differences in clinical characteristics, ancillary test results, and underlying tumor frequency between the antibody types were analyzed using the chi-square test for categorical variables and the Kruskall–Wallis test for continuous variables. The data are expressed as the mean ± standard deviation (SD) for continuous variables and as counts (percentages) for categorical variables. Statistical analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA), and significance was set at $p < 0.05$.

3. Results

3.1. Prevalence of autoimmune encephalopathy and associated antibodies

Between Jan. 2013, and Dec. 2014, samples from 1699 patients with idiopathic encephalopathy, referred from 70 hospitals across Korea (Fig. 1), were screened for antineuronal antibodies. Antibodies were detected in 109 patients, but five of these patients were later excluded due to an alternative diagnosis: two patients with anti-Yo antibodies were diagnosed with Creutzfeldt–Jakob disease and multiple cerebral infarction, two patients with anti-amphiphysin antibodies were diagnosed with anti-GQ1b-mediated Bickerstaff's encephalitis and metabolic encephalopathy, and one other patient with anti-Ma2 antibodies was diagnosed with metabolic encephalopathy. Finally, 104 patients (6.12%) with antibody-associated autoimmune encephalopathy were analyzed. Overall, the mean age of the patients at symptom onset was 40 years (SD 21, range 9 months–81 years), 55 (52.9%) were male, and the mean disease duration was 87.5 days (SD 175, range 1–822 days). Thirty-three patients were seen by the study investigators, while the others were seen by the referring physicians. Twenty-one of these patients (6 anti-NMDAR, 8 anti-LGI1, 2 anti-GABAb, 4 anti-Caspr2, and 1 anti-amphiphysin) were reported previously (Lim et al., 2014; Shin et al., 2013; Kim et al., 2014; Sunwoo et al., 2015; Moon et al., 2014).

The prevalence of the antibodies is listed in Table 1. One patient with visual hallucination, ataxia, and polyneuropathy exhibited both anti-NMDAR and anti-Hu antibodies. Because the patient's CSF produced intense immunostaining not only to the neuropil, but also to the neuronal nuclei of the rat hippocampus, he was included for both anti-NMDAR and classic paraneoplastic antibody group. ASAbs were detected in 89 (5.24%) patients; anti-NMDAR antibodies were the most common (n = 57, 3.35%), followed by anti-LGI1 antibodies (n = 24, 1.41%). Other ASAbs were identified in eight patients (0.47%): four patients had anti-Caspr2 antibodies, three patients had anti-GABAb antibodies,