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서울대학교병원 신경과

Paraneoplastic and autoimmune encephalitis

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This presentation provides an update on classic paraneoplastic syndromes (anti-Hu, Yo, Ri, Ma2, CV2/CRMP5, and amphiphysin antibodies) and autoimmune encephalitis associated with antibodies against synaptic proteins (anti-NMDA, AMPA, GABA-B receptors, LGI1, and Caspr antibodies) (Table 1). Many of the classic paraneoplastic antibodies target intracellular antigens and mediate cytotoxic T-cell responses. They are associated with systemic cancers, and symptoms are often resistant to immunotherapy. The autoimmune encephalitis syndromes are associated with antibodies against extracellular synaptic epitopes, often mediated by direct antibody-mediated pathogenesis, and thus responsive to immunotherapy. They occur with or without cancer and can relapse. Among them, anti-NMDA receptor encephalitis is the most common type of autoimmune encephalitis and presents with psychiatric symptoms followed by memory impairment, speech dysfunction, seizure, orofacial/limb dyskinesia, decreased consciousness, autonomic instability, and central hypoventilation. All the patients have the antibody in CSF, and about half of them have ovarian teratoma. The anti-LGI1 antibody is the second most common, and presents with limbic encephalitis. Faciobrachial dystonic seizure and hyponatremia are the distinguishing features of this syndrome. Nevertheless, the antigens have not been disclosed in many cases of autoimmune encephalitis, and the blind screening of antibodies is available for these conditions. Korea autoimmune synaptic and paraneoplastic encephalitis registry (KASPER) is in operation to discover new antigens and more therapeutic options. The spectrum of paraneoplastic and autoimmune synaptic encephalitis is broad, and patient-specific treatments are necessary because of various pathogenesis and therapeutic responses. Immunotherapies include the first-line immunotherapy (IVIg, and steroid), the second-line immunotherapy (Rituximab, cyclophosphamide), and other maintenance immunosuppressants. In autoimmune synaptic encephalitis, the second-line immunotherapy can rescue the patients who are refractory to the first-line immunotherapy. The update in pathogenesis and treatment protocols will be discussed.

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Table 1. Paraneoplastic and autoimmune encephalitis

Antigen	Syndromes	Common tumors
Hu (ANNA1)	Encephalomyelitis, limbic encephalitis, sensory polyneuropathy, cerebellar degeneration, limbic encephalitis	Small cell lung cancer (SCLC), neuroendocrine tumors
Yo (PCA1)	cerebellar degeneration	Ovary, Breast
CV2/CRMP5	Limbic encephalitis, optic neuritis, retinopathy, sensory motor polyneuropathy, chorea	SCLC, thymoma
Ri (ANNA2)	Opsoclonus myoclonus, ataxia, brainstem encephalitis	Breast, gynecologic, SCLC
Ma2/Ta	Brainstem encephalitis (midbrain), Limbic encephalitis	Testicular, lung, breast
Amphiphysin	Stiff person syndrome, encephalomyelitis, limbic encephalitis, polyneuropathy	Breast, SCLC
NMDA receptor	Psychiatric symptoms, seizure, memory impairment, speech dysfunction, movement disorder, decreased consciousness, autonomic instability, central hypoventilation	~50% Ovarian teratoma
LGI1 (VGKC)	Limbic encephalitis, hyponatremia, seizure, faciobrachial dystonic seizure	<20% thymus, lung
Caspr2 (VGKC)	Limbic encephalitis, peripheral nerve hyperexcitability (Morvan syndrome)	Limited
GABA-B receptor	Limbic encephalitis, seizure	~70% SCLC
AMPA receptor	Limbic encephalitis, psychiatric symptom	~70% lung, breast, thymus