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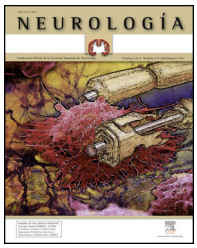

REVIEW ARTICLE

Clinical spectrum and diagnostic value of antibodies against the potassium channel-related protein complex☆

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Abstract
Introduction: Antibodies against a protein complex that includes voltage-gated potassium channels (VGKC) have been reported in patients with limbic encephalitis, peripheral nerve hyperexcitability, Morvan's syndrome, and a large variety of neurological syndromes.
Review summary: In this article, a review is presented of the syndromes associated with antibodies against VGKC-related proteins and the main antigens of this protein complex, the proteins LGI1 (leucine rich glioma inactivated protein 1) and Caspr2 (contactin-associated protein-like 2). The conceptual problems and clinical implications of the description of antibodies against VGKC-related proteins other than LGI1 and Caspr2 are also discussed.

Although initial studies indicated the occurrence of antibodies against VGKC, recent investigations have shown that the main antigens are a neuronal secreted protein known as LGI1 which modulates synaptic excitability, and a protein called Caspr2 located on the cell surface and processes of neurons of different brain regions, and at the juxtaparanodal region of myelinated axons. While antibodies against LGI1 preferentially associate with classical limbic encephalitis, antibodies against Caspr2 associate with a wider spectrum of symptoms, including Morvan's syndrome, peripheral nerve hyperexcitability or neuromyotonia, and limbic or more extensive encephalitis. In addition there are reports of patients with antibodies against VGKC-related proteins that are different from LGI1 or Caspr2. In these cases, the identity and location of the antigens are unknown, the syndrome association is not specific, and the response to treatment uncertain.

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Conclusions: The discovery of antigens such as LGI1 and Caspr2 has resulted in a clinical and molecular definition of the broad group of diseases previously attributed to antibodies against VGKC. Considering the literature that describes the presence of antibodies against VGKC other than LGI1 and Caspr2 proteins, we propose a practical algorithm for the diagnosis and treatment of these patients.

PALABRAS CLAVE
Encefalitis;
Canales de potasio;
Anticuerpos;
Autoinmune

Espectro clínico y valor diagnóstico de los anticuerpos contra el complejo proteico asociado a canales de potasio

Resumen
Introducción: Los anticuerpos contra un complejo proteico que incluye a los canales de potasio dependientes de voltaje (CKVD) se han descrito en pacientes con encefalitis límbica, hiperexcitabilidad del nervio periférico, síndrome de Morvan, así como en un creciente grupo de síndromes neurológicos.
Desarrollo: En este artículo revisamos los síndromes asociados a anticuerpos contra proteínas relacionadas con los CKVD y los 2 antígenos principales de este complejo, las proteínas leucine rich glioma inactivated protein 1 (LGI1) y contactin-associated protein-like 2 (Caspr2). Así mismo describimos los problemas conceptuales y las implicaciones diagnósticas de la descripción de anticuerpos contra CKVD diferentes de LGI1 y Caspr2.

Aunque inicialmente se consideró que existían anticuerpos dirigidos contra CKVD, recientemente se ha identificado que, en la mayor parte de los casos, los antígenos son una proteína neuronal secretada denominada LGI1, involucrada en el control de la excitabilidad sináptica, y la proteína Caspr2, localizada en la superficie neuronal de varias regiones cerebrales y en la región yuxtaparanodal de axones mielinizados. Mientras que los anticuerpos contra LGI1 se asocian preferentemente a un cuadro clásico de encefalitis límbica, los anticuerpos contra Caspr2 muestran un espectro clínico más amplio, incluyendo el síndrome de Morvan, la hiperexcitabilidad del nervio periférico o neuromiotonía, o una encefalitis límbica o difusa. Existen además casos descritos de pacientes con anticuerpos contra el complejo CKVD que no tienen anticuerpos contra LGI1 o Caspr2. En estos casos, la identidad y la localización de los antígenos es desconocida, la asociación sindrómica inespecífica y la respuesta al tratamiento, incierta.
Conclusiones: El descubrimiento de los antígenos LG1 y Caspr2 ha permitido delimitar clínica y molecularmente el amplio grupo de síndromes previamente atribuidos a anticuerpos contra CKVD. Frente a la literatura que describe la presencia de anticuerpos contra CKVD diferentes a LGI1 y Caspr2, proponemos un algoritmo práctico para el diagnóstico y el tratamiento de estos pacientes.

Introduction

Voltage-gated potassium channel (VGKC) antibodies have been identified in a wide range of neurological syndromes involving the central and peripheral nervous systems in both adults[1] and children.[2] These antibodies were initially thought to target epitopes of the VGKC; however, research in the past few years indicates that most of them are directed to leucine-rich glioma inactivated protein 1 (LGI1)[3] and contactin-associated protein-like 2 (CASPR2).[3,4] Furthermore, recent studies have described a group of patients testing positive for antibodies against VGKC-complex proteins but negative for Caspr2 and LGI1.[5,6]

Anti-LGI1 antibodies are present in limbic encephalitis,[3] while anti-Caspr2 antibodies may be associated with encephalitis,[3,4] peripheral nerve hyperexcitability (also known as acquired neuromyotonia or Isaacs syndrome),[7] or a combination of both (Morvan syndrome).[3–6] These 2 proteins are well characterised, and alterations in them provide the pathophysiological mechanism for the clinical symptoms of each type of autoimmune response. In contrast, target antigens in patients with antibodies against VGKC-complex proteins, but testing negative for LGI1 and Caspr2, are unknown.[8] Patients with these antibodies form a heterogeneous and increasing population. For the above reasons, current research focuses on determining the clinical significance and pathogenic mechanisms of these antibodies (Table 1). The present review article aims to clarify these questions related to the clinical and pathological spectra and describe the syndromes associated with these antibodies.

Identification of target antigens in patients with antibodies initially attributed to voltage-gated potassium channels

The term 'VGKC antibody' has been used to denote antibodies detected with radioimmunoassay (RIA) that labels the