Paediatr Croat. 2012;56:119-124

AUTOANTIBODIES IN ENCEPHALOPATHIES

ANGELA VINCENT*

There have been several advances in identifying antibody-mediated central nervous system diseases. These are associated with the presence of antibodies to neuronal or glial cell surface proteins, principally ion channels, receptors and associated proteins. Although first described in adults, they are now being identified also in children of all ages. These conditions are important to recognise because they often respond to immunotherapies.

Descriptors: AUTOANTIBODIES; CHILD; CENTRAL NERVOUS SYSTEM

INTRODUCTION

There is a growing family of antibodies that bind to proteins on the cell surface of neurons (VGKC-complex proteins LGI1 and CASPR2, NMDA, AMPA, GABAb and Gly receptors) or glia (Aquaporin-4, MOG). Many of the patients do not have tumours and many appear to have a monophasic course; others may relapse and require ongoing immunosuppression (1).

These antibodies contrast with the "onconeural" antibodies which are found predominantly in patients with paraneoplastic neurological diseases. These conditions generally are not responsive to immunotherapies, although tumour removal may stabilise their neurological signs. They will not be considered further here.

The number of patients with the new cell-surface antibodies are not yet clear, but in the UK we are identifying these antibodies in around 400 patients *per* year, mainly in adults, representing 5-10 *per* million *per* year. Nevertheless, there are other patients with similar syndromes in whom the current tests are negative, but who might respond to immunotherapies, and this includes many children with possible immune-mediated central nervous system (CNS) diseases. A recent review and guidelines on approaches to identify patients with autoimmune forms of encephalitis may be helpful (2). Here the main forms of antibody-associated/mediated syndromes will be described briefly as they occur in adults, with reference to paediatric cases as appropriate.

Antibodies associated with limbic encephalitis

Limbic encephalitis (LE) typically presents with acute or subacute onset of memory loss, confusion and seizures, with high signal in the mediotemporal lobes on magnetic resonance imaging (MRI), and pleocytosis or high protein in the cerebrospinal fluid (CSF) (Table 1). The identification of antibodies to the VGKC-complex antigens (LGI1, CASPR2 and contactin-2), AMPAR, $GABA_BR$, GAD or NMDAR is now routine in many laboratories (1).

VGKCs are found throughout the brain and are important in restoring the membrane potential during hyperpolarisation. VGKC-antibodies were initially identified using a radioimmunoprecipitation assay of VGKC complexes solubilised from mammalian brain tissue. These antibodies were found in patients with neuromyotonia, and also in the rare Morvan's syndrome which comprises neuromyotonia, autonomic and CNS involvement with insomnia (3). It became clear that the same antibodies, apparently, were detected in patients with LE (4, 5) and more recently in patients with faciobrachial dystonic seizures (FBDS) (6). VGKC-antibodies do not, however, bind directly to the VGKCs themselves but to components of a complex of membrane-associated proteins that include the VGCKs (Figure 1). Antibodies to any of these proteins can be shown to immunoprecipitate VGKCs (7).

The main VGKC-complex proteins identified to date are leucine-rich glioma inactivated protein 1 (LGI1) (7, 8) and contactin-associated protein 2 (CASPR2) (7). However, because not all the complex-proteins are known, we continue to use radioimmunoprecipitation for routine screening of patients. The specificity for LGI1, CASPR2 or contactin-2 can then be determined, if required, by a cell-based assay. This relies on the expression of the specific antigen in a cell-line and detection of the antibodies binding to the antigen on the surface of the cell using indirect immunofluorescence. Figure 2 illustrates how this is done.

Limbic encephalitis with antibodies to voltage gated potassium channel-complex antibodies (VGKC-complex-Abs)

Patients with VGKC-complex-Abs typically present with memory loss, confu-

* Neuroimmunology Group, Nuffield Department of Clinical Neurosciences, Level 5/6 John Radcliffe Hospital, Oxford OX3 9DU

Correspondence to:
Angela Vincent, MD, PhD, Neuroimmunology Group, Nuffield Department of Clinical Neurosciences, Level 5/6 John Radcliffe Hospital, Oxford OX3 9DU, e-mail: Angela.vincent@ndcn.ox.ac.uk

Table 1. *Different forms of limbic encephalitis*
Tablica 1. *Različiti oblici limbičnog encefalitisa*

	Helpful clinical features Korisna klinička obilježja	Which antibodies Koja antitijela	Tumour associations Udruženost s tumorima	In children Kod djece
LIMBIC ENCEPHALITIS LIMBIČNI ENCEFALITIS Subacute memory loss, psychiatric or behavioural disturbance, seizures Subakutni gubitak pamćenja, psihijatrijski poremećaj ili poremećaj ponašanja, konvulzije MRI typically shows high signal in the medial temporal lobes (MTL) MRI znakovito pokazuje visok signal u medijalnim temporalnim režnjevima CSF variable but can be pleocytosis, mildly raised protein or oligoclonal bands Nalaz likvora varijabilan, može se naći pleocitoza, blago povišene bjelančevine ili oligoklonske vrpce	Serum hyponatremia commonly noted in adults Hiponatremija u serumu često se vidi kod odraslih	VGKC-complex antibodies; commonly directed against LGI1 Antitijela VGKC-kompleksa; često usmjerena protiv LGI1	Tumours uncommon Tumori rijetki	Good response to immunotherapies Dobar odgovor na imunoterapije Only a few cases reported in children, but not LGI1 Samo nekoliko slučajeva opisano u djece, ali ne LGI1
	Rapidly progressing LE with features of acute psychosis Brzo progredirajući LE s obilježjima akutne psihoze	AMPA receptor (GluR 1/2) Receptor AMPA (GluR 1/2)	Often paraneoplastic; SCLC, breast, thymoma (70%) Često paraneoplastični; SCLC, dojka, timom (70%)	Not reported in children to date Dosad nije opisan u djece
	Seziures as the predominant symptom, usually of temporal lobe onset with secondary generalisation Konvulzije kao prevladavajući symptom, obično nastaju u temporalnom režnju sa sekundarnom generalizacijom	$GABA_BR$ $GABA_BR$	Often paraneoplastic: SCLC (47%) Često paraneoplastični: SCLC (47%)	Not reported in children to date Dosad nije opisan u djece
	Temporal lobe seizures with less evident cognitive involvement Konvulzije u temporalnom režnju s manje primjetljivo zahvaćenom spoznajnom funkcijom	Glutamic acid decarboxylase Dekarboksilaza glutamične kiseline	Tumours rare; diabetes Tumori rijetki; dijabetes	Children with GAD antibodies and LE have been reported Opisana su djeca antitijelima GAD i LE
FACIOBRACHIAL DYSTONIC SEIZURES FACIOBRAHIJALNE DISTONIČNE KONVULZIJE	Brief (few seconds), frequent (50/day) dystonic seizures. Usually leads into limbic encephalitis unless treated first Kratkotrajne (nekoliko sekunda) česte (50/dan) distonične konvulzije. Ako se ne liječi na vrijeme, obično dovodi do limbičnog encefalitisa	VGKC-complex antibodies, usually LGI1 Antitijela VGKC-kompleksa, obično LGI1	None described to date Dosad nijedan opisan	Immunotherapy responsive and often poor anti-epileptic drug responses Odgovara na imunoterapiju i često slab odgovor na antiepileptike Not reported in children to date Dosad nije opisan u djece

sion and seizures (4-8). Many of them have high titres of VGKC-complex-Abs (>400 pM) but lower levels can be found in patients with typical LE (4-7), although the specificity for LE of the lower VGKC antibodies (<400 pM) in our experience is less high. One clinical feature that is helpful in LE with these antibodies is serum hyponatremia found in up to 60% (4, 5, 6, 8). On the other hand, the CSF is often normal and oligoclonal bands uncommon (4) and the MRI may not show the typical high signal.

These patients usually do well with immunotherapies that include intravenous methyl-prednisone, plasma exchange, intravenous immunoglobulins (IvIg) and other drugs if required. The antibody levels often fall rapidly (4-6), the hyponatremia resolves and the seizures cease. However, the patients are often left with hippocampal atrophy and the cognitive improvement is slower, although often substantial (5, 7). It has been proposed that some cases of adult onset hippocampal sclerosis are secondary to a previous LE (9).

LGI1 antibodies are most common, and at highest titres, in patients with typical LE usually without a tumour (7, 8). CASPR2 antibodies are more common in patients with neuromyotonia or Morvan's syndrome (3, 7), and sometimes coexist with contactin-2 antibodies or LGI1 antibodies at lower titres (3). CASPR2 antibodies tend to be associated with thymomas and sometimes with previous myasthenia gravis (3, 7). But none of these distinctions is absolute. Not many children have been reported with VGKC-antibody associated LE but these antibodies were found retrospectively in children presenting with status epilepticus in one centre (10).

Faciobrachial dystonic seizures and LGI1/VGKC-complex-Abs

Adult patients presenting with dystonic seizures affecting most often one arm and one side of the face have been found to have raised levels of VGKC-antibodies, sometimes very high titre. These 'faciobrachial dystonic' seizures (FBDS) are very brief (a few seconds) and can occur up to 200 times a day. Some patients have no cognitive problems at onset but develop them subsequently. In others, the FBDS or 'tonic seizures' are only identified during LE (6, 8). Importantly, these seizures respond very well to immunotherapies but often show a poor response with adverse effects to typical antiepileptic drugs (6).

Limbic encephalitis with other antibodies

Antibodies to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR-Abs) do not appear to be very common in LE. They occur in patients with a typical LE, although often a more psychiatric phenotype. There is a high tumour incidence in adults and their presence in children has not been reported to date. The reported adult cases have a tendency to relapse following apparent response to immunotherapies (11).

Antibodies to $GABA_B$ receptor antibodies ($GABA_B$R-Abs) are also seen in a form of LE, but here the most frequent presentation is temporal lobe seizures (12). They have not been reported in children but there may be overlap with other antibodies such as GAD. Many of the reported patients had tumours and responded to immunotherapies with a tendency to relapse (12).

Antibodies to glutamic acid decarboxylase (GAD) are sometimes present in patients with a form of LE characterised by temporal lobe epilepsy. Adult patients tend to be younger females and present with seizures without apparent memory loss (13), but cognitive changes can be demonstrated on formal testing. Compared with VGKC-antibodies in LE, the GAD-antibody patients often do not do well, and antibody titres are still high following treatments (13). GAD-antibodies in LE have been reported in children (14, 15).

Encephalitis with NMDAR antibodies

N-methyl D-aspartate receptors are ligand-gated ion channels, known to be major mediators of excitatory neurotransmission in the CNS (Table 2). Antibodies to the NMDAR (predominantly the NR1 subunit) were first described in a form of encephalitis with ovarian teratoma (16-18). The patients often present first with psychosis or behavioural disturbance, cognitive problems and seizures. Headache and fever are not infrequent, contrasting with typical LE. MRI findings are often normal and when present are usually outside the medial temporal lobes (cerebral cortex, overlying meninges, basal ganglia) (16-18).

Over the next 10 to 20 days, the clinical features progress to include dyskinesias (orofacial grimacing, dystonic posturing and choreoathetoid movements), autonomic instability and reduction in consciousness, often requiring ventilatory support. At onset, pleocytosis is common and oligoclonal bands are rare. As the disease progresses, the cells tend to disappear but oligoclonal bands may appear. NMDAR antibodies are present in the serum and CSF (17). Although the sera titrate out further than the CSFs, there is substantial intrathecal synthesis of the NMDAR antibodies in most patients. This implies that during the disease, NMDAR-antibody specific B cells or plasma cells migrate into the CNS and synthesise the specific antibodies within that compartment. A recent review covers the clinical and paraclinical findings in more detail (18).

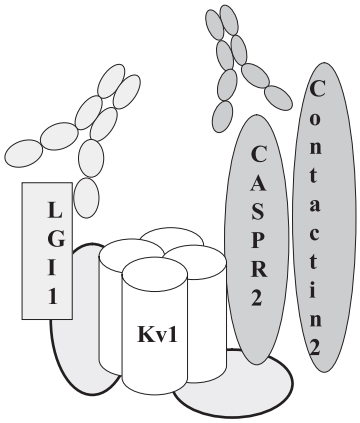

Figure 1. *Diagram to represent the VGKC-complex. This consists of the VGKC Kv1 (white) subunits and other proteins that are tightly complexed with the VGKC in vivo. Antibodies to these proteins can immunoprecipitate VGKCs and are now called VGKC-complex antibodies. The figure illustrates the known antigenic targets which are LGI1, CASPR2 and contactin-2. These proteins are complexed via other proteins (grey), which are not well defined. In addition, binding of LGI1 to other key proteins such as ADAM22 and ADAM23 may be important (8). However, it is important to appreciate that the full spectrum of the complexed proteins and their disease associations are not yet clear. For instance, CASPR2 antibodies have been reported in a few patients with non-paraneoplastic cerebellar ataxia (34).*
Slika 1. *Dijagram prikazuje VGKC-kompleks. On se sastoji od podjedinica VGKC Kv1 (bijelo) i drugih bjelančevina koje se čvrsto povezuju s VGKC in vivo. Antitijela na ove bjelančevine mogu imunoprecipitirati VGKC i tada se nazivaju antitijelima VGKC-kompleksa. Slika prikazuje poznate antigene ciljeve, LGI1, CASPR2 i kontaktin-2. Ove se bjelančevine povezuju putem drugih bjelančevina (sivo), koje još nisu potpuno definirane. Uz to, vezanje LGI1 za druge ključne bjelančevine kao što su ADAM22 i ADAM23 također bi moglo biti važno (8). Međutim, treba uzeti u obzir da čitav spektar povezanih bjelančevina i njihove udruženosti s bolestima nije razjašnjen. Primjerice, antitijela CASPR2 opisana su u nekoliko bolesnika s ne-paraneoplastičnom cerebelarnom ataksijom (34).*

Although first described with ovarian teratomas, many patients, both male and female, are being identified in whom no tumour is ever found (17), and tumours are very infrequent in young children (17-19). Compared with most patients with limbic encephalitis and neuronal surface antibodies, NMDAR-antibody patients are often resistant to treatments. Removal of the tumour if present, and repeated scanning of the ovaries when not identified, is essential. High dose steroids, plasma exchange and IvIg are used in most patients, and in many cyclophosphamide and rituximab may be required. Even with these treatments, the patients can spend many weeks or months in intensive care (16-18). Nevertheless, many patients eventually make a good recovery, although they may be left with cognitive impairment including amnesia, and relapses are being reported in a number of patients suggesting that longer-term immunosuppression may be required in some (18). NMDAR-antibodies are now being identified regularly in children with this syndrome, including some who would otherwise be given the diagnosis of encephalitis lethargic (19-21).

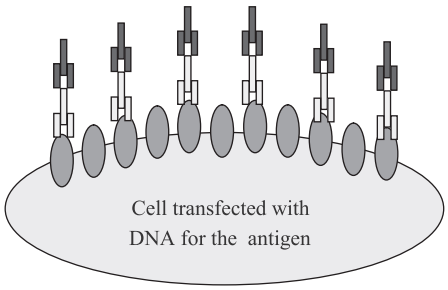

Figure 2. *Measuring antibodies by binding to cells expressing the antigen. In order to demonstrate antibodies to antigens such as LGI1, CASPR2, NMDAR, AQP4, GLYR and other membrane proteins, cell based assays are beginning to be widely used. The cells are transfected to express the antigen (green). Serum or CSF is applied to the surface of the cells, and any bound IgG antibodies (yellow) detected with a fluorescently-labelled anti-human IgG (red). If live cells (not fixed) are used, they measure antibodies that bind only to the extracellular epitopes and are thus likely to be pathogenic in vivo.*
Slika 2. *Mjerenje antitijela vezanjem stanica koje izražavaju antigen. Stanični testovi sve se više primjenjuju za dokazivanje antitijela na antigene kao što su LGI1, CASPR2, NMDAR, AQP4, GLYR i druge membranske bjelančevine. Provodi se transfekcija stanica kako bi one izrazile antigen (zeleno). Na površinu stanice nanosi se serum ili cerebrospinalni likvor te se sva vezana IgG antitijela (žuto) otkrivaju fluorescentno obilježenim anti-humanim IgG (crveno). Ako se rabe žive stanice (ne fiksirane), one mjere antitijela koja vežu samo izvanstanične epitope pa su stoga vjerojatno patogene in vivo.*

Morvan's syndrome

The combination of neuromyotonia (muscle fasciculations and cramps), autonomic disturbance and insomnia, Morvan's syndrome, is rare but can occur very occasionally in children (22). In adults it has been misdiagnosed as schizophrenia (18). The VGKC-complex antibodies are directed most often to CASPR2 but LGI1 antibodies may also be present at lower titres (3). Morvan's syndrome can present in patients with recurrent or aggressive thymomas, and coexisting myasthenia (3).

Table 2. *Features of NMDAR-antibody encephalitis*
Tablica 2. *Obilježja encefalitisa s NMDAR-antitijelima*

Clinical features Klinička obilježja	Demographics Demografska obilježja	Tumours and treatment responses Tumori i odgovor na liječenje
May have prodromal viral-like symptoms and varied preceding infections fairly common in children. Headache and fever quite common. Može imati prodromne virusu slične simptome i razne prethodne infekcije koje su prilično česte kod djece. Često je prisutna glavobolja i vrućica. Neurological presentation with psychosis, seizures, cognitive and behavioural changes evolving over days to weeks to choreoatheroid movement disorders, orofacial dyskinesia, dysautonomia, mutism and catatonia. Neurološke manifestacije sa psihozom, konvulzijama, spoznajnim poremećajem i promjenama ponašanja, koje se razvijaju danima ili tjednima sve do koreoateroidnih poremećaja kretanja, orofacijalne diskinezije, disautonomije, mutizma i katatonije. MRI: normal, mild abnormalities usually outside the medial temporal lobes MRI: normalan, blaže nenormalnosti obično izvan medijalnih temporalnih režnjeva EEG: generalised slowing, possible epileptiform activity EEG: generalizirana usporenost, moguća epileptiformna aktivnost CSF: lymphocytic pleocytosis, possible raised protein, oligoclonal bands appear over time Likvor: limfocitna pleocitoza, moguće povišene bjelančevine, s vremenom se pojave oligoklonske vrpce	Younger adult females most common, but also adult males and high proportion of children of both sexes, some less than one year starting from less than one year-old. Najčešće mlađe odrasle ženske osobe, ali isto tako i odrasle muške osobe te visok udio djece obaju spolova, počev od dobi ispod jedne godine.	Ovarian teratoma Teratom jajnika Up to 50% of young female adults, but much rarer in children Do 50% mlađih ženskih odraslih osoba, ali znatno rjeđe u djece Immunotherapies appear to be helpful but improvement can take weeks to months Izgleda da su imunoterapije korisne, ali mogu proći tjedni ili mjeseci dok nastupi poboljšanje Substantial recovery can occur eventually Na kraju može doći do znatnog oporavka

Antibody-associated encephalomyelopathies

Neuromyelitis optica (NMO)

Although not strictly an encephalomyelopathy, the identification of antibodies to aquaporin-4 (AQP4) in this condition has made a substantial impact on the diagnosis and clinical care of patients who previously could be misdiagnosed as having multiple sclerosis (reviewed in ref. 23). The antibodies are found in over 60-80% of patients with NMO depending partly on the assays used (24). The relapses in the disease need to be treated promptly, and maintenance therapies with azathioprine or other immunosuppressants are commonly used in the hope of preventing the relapses and permanent disability. This is a condition that is clearly present in children (25).

Stiff person syndrome (SPS) and progressive encephalomyelopathy with rigidity and myoclonus (PERM)

SPS is a rare disorder characterized by muscle rigidity and episodic spasms, usually affecting the lumbar, thoracic, paraspinal and proximal leg muscles. Patients are often thought to have a non-organic disorder. Antibodies to GAD are typically found (26), or to amphiphysin in forms associated with neoplasms, which are rarer still. EMG demonstrates continuous low frequency firing of motor units. Treatment includes medication directed against the muscle spasm and rigidity such as benzodiazepines and baclofen, antiepileptics, and immunotherapies (26), which are variably effective but probably need to be continued for many years.

Antibodies to GAD are also found in progressive encephalomyelitis with rigidity and myoclonus (PERM) as well as other forms of SPS such as stiff limb syndrome. In patients with PERM, rigidity and spasms are accompanied by brainstem signs such as oculomotor disturbance, painful touch or sound-sensitive spasms, generalised myoclonus and autonomic features (26). Progression of symptoms can be variable but in some patients can lead to rapid deterioration and death. The CSF may show lymphocytic pleocytosis and oligoclonal bands, but imaging is often uninformative. EMG findings and treatment approaches are similar to those for SPS (26). Antibodies to the glycine receptor alpha1 subunit have now been identified in some patients with PERM and these patients appear to respond well to immunotherapies (27-29). One patient had a thymoma and made a remarkable recovery after surgery and immunotherapy (29). A few children with these antibodies are beginning to be identified (A Vincent unpublished).

Practical considerations for paediatrics

The number of children reported with the antibodies described here is still very small but increasing. Children with NMDAR antibodies are now being identified by many centres, and this is a diagnosis that should not be missed, even if described initially as encephalitis lethargic. AQP4 antibodies are now searched for routinely in children with demyelinating conditions that could represent NMO, and are found in a proportion but this seems to be lower than in adults. Antibodies to myelin-oligodendrocyte glycoprotein (MOG), originally thought to be mainly found in ADEM, may also be helpful in patients who present with an NMO-like phenotype (30, 31).

There are beginning to be commercial assays for these antibodies, and most will recommend testing of serum, although it is always of interest to compare it with CSF. Only in very rare cases are the CSF levels positive while serum levels (usually measured after dilution) are undetectable. Nevertheless, there is often intrathecal synthesis of the specific antibody resulting from the presence of plasma cells in the intrathecal compartment. This may or may not correlate with the presence of oligoclonal bands, and whether the bands are related to the specific antibody is not yet clear. It is always best to check with the laboratory before deciding which samples to send for testing.

The specificity of the antibodies should be high if measured by an experienced laboratory, but as more and more patients are identified there are beginning to be some surprises. Thus, some patients may have very low titres of antibody which may not be clinically relevant, or have more than one antibody (e.g. 32). Moreover, a proportion of patients with acute encephalitis have antibodies (33), and even some with defined viral forms of encephalitis (AV unpublished data). This

Table 3. *Other antibody-associated diseases with immunotherapy responses*
Tablica 3. *Ostale bolesti udružene s antitijelima i odgovor na imunoterapiju*

	Clinical features Klinička obilježja	Investigations Pretrage
Neuromyelitis optica with aquaporin-4 antibodies Optički neuromijelitis s antitijelima akvaporin-4	Optic neuritis, pain, sensory disturbance, paralysis or combinations thereof Optički neuritis, bolovi, senzorni poremećaj, paraliza ili njihova kombinacija	MRI: inflammation of optic nerve and/or longitudinal extensive transverse myelitis MRI: upala očnog živca i/ili longitudinalni ekstenzivni transverzalni mijelitis Can be brain lesions but not fulfilling criteria for multiple sclerosis Moguće su promjene na mozgu, ali ne ispunjavaju kriterije za multiplu sklerozu CSF: oligoclonal bands not common CSF: oligoklonske vrpce nisu česte
Stiff person syndrome with glutamic acid decarboxylase antibodies Sindrom ukočene osobe s antitijelima dekarboksilaze glutamične kiseline	Stiffness, rigidity, CNS involvement not uncommon Ukočenost, krutost, nije rijetka zahvaćenost SŽS Absent during sleep Odsutan kod spavanja May have IDDM and/or other autoantibodies Može imati IDDM i/ili druga antitijela	MRI: normal, non-specific MRI: normalan, nespecifičan EMG: continuous motor unit activity in affected muscles EMG: kontinuirana aktivnost motornih jedinica u zahvaćenim mišićima CSF: oligoclonal bands common but not invariable Likvor: oligoklonske vrpce su česte, ali ne uvijek prisutne
Progressive encephalomyelitis with rigidity and myoclonus with glycine receptor or GAD antibodies (tumours infrequent) Progresivni encefalomijelitis uz krutost i mioklonus s antitijelima receptora glicina ili antitijelima GAD (tumori rijetki)	Rigidity, myoclonus, brainstem and cranial nerve involvement Krutost, mioklonus, zahvaćeni živci moždanog debla i vrata Progressive and severe or relapsing remitting Progresivni i težak ili relapsirajući remitirajući Has been described in a child Opisan u djeteta	MRI: normal MRI: normalan EMG: as for SPS EMG: kao za SPS CSF: lymphocytic pleocytosis, oligoclonal bands not invariable Likvor: limfocitna pleocitoza, oligoklonske vrpce nisu uvijek prisutne
Morvans syndrome (can be associated with thymomas and myasthenia gravis) with VGKC--complex antibodies. Morvansov sindrom (može biti udružen s timomima i mijastenijom gravis)	Fasciculations, stiffness and muscle cramps Fascikulacije, ukočenost i grčevi mišića Peripheral nerve hyperxcitability Hiperekscitabilnost perifernih živaca Autonomic and CNS dysfunction, insomnia Disfunkcija autonomnog i SŽS, besanica	EEG: generalised slowing EEG: generalizirana usporenost EMG: doublet, triplet, multiplet single unit discharges EMG: dvostruka, trostruka, višestruka pojedinačna izbijanja MRI: usually normal MRI: obično normalan CSF: not usually tested Likvor: obično se ne ispituje

latter observation, although rare, suggests that in some patients the antibodies may occur secondarily to other disease processes; the clinician needs to bear this in mind when assessing the relevance of serological findings.

Conflicts

A.V. and the Department of Clinical Neurology in Oxford receive royalties and payments for Ab assays. A.V. is the inventor on patent application WO/2010/046716 entitled "Neurological Autoimmune Disorders". The patent has been licensed to Euroimmun AG for the development of assays for LGI1 and other VGKC-complex Abs. A.V. acts as a paid consultant for Athena Diagnostics, and is employed by Oxford University and University College London. A.V and S.R.I. may receive royalties for testing of VGKC complex Abs.

REFERENCES

1. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 2011;10:759-72.
2. Zuliani L, Graus F, Giometto B, Bien CG, Vincent A. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012;83:638-45.
3. Irani SR, Pettingill P, Kleopa KA, et al. Morvan Syndrome clinical and serological observations in 29 cases. Ann Neurol. 2012 Mar 9. Doi: 10.1002/ana.23577.
4. Buckley C, Oger J, Clover L, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol. 2001;50:73-8.
5. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701-12.
6. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1-antibody limbic encephalitis. Ann Neurol. 2011;69:892-900.
7. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133:2734-48.
8. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776-85.
9. Bien CG, Urbach H, Schramm J, et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. Neurology. 2007;69:1236-44.
10. Suleiman J, Brenner T, Gill D, Brilot F, Antony J, Vincent A, Lang B, Dale RC. VGKC antibodies in pediatric encephalitis presenting with status epilepticus. Neurology. 2011;76:1252-5.
11. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424-34.
12. Lancaster E, Lai M, Peng X, et al. Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9:67-76.
13. Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010;67:470-8.
14. Haberlandt E, Bast T, Ebner A, et al. Limbic encephalitis in children and adolescents. Arch Dis Child. 2011;96:186-91.
15. Korff CM, Parvex P, Cimasoni L, et al. Encephalitis associated with glutamic acid decarboxylase autoantibodies in a child: a treatable condition? Arch Neurol. 2011;68:1065-8.
16. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091-8.
17. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133:1655-67.
18. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with

anti-NMDAR encephalitis. Lancet Neurol. 2011; 10:63-74.
19. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11-8.
20. Florance-Ryan N, Dalmau J. Update on anti-N-methyl-D-aspartate receptor encephalitis in children and adolescents. Curr Opin Pediatr. 2010;22:739-44.
21. Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, Lang B, Vincent A. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol. 2009;66:704-9.
22. Bunoza B, Barišić N, Lehman I, Vincent A, Galić S, Novak M, Slaviček J, Puretić Z. Juvenile myasthenia gravis associated with autoimmune channelopathy and mixed connective tissue disease. Eur J Paediatr Neurol. 2011;15 (Suppl 1):S55.
23. Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. Nat Rev Neurol. 2010;6:383-92.
24. Waters PJ, McKeon A, Leite MI, Rajasekharan S, Lennon VA, Villalobos A, Palace J, Mandrekar JN, Vincent A, Bar-Or A, Pittock SJ. Serologic diagnosis of NMO: A multicenter comparison of aquaporin-4-IgG assays. Neurology. 2012;78:665-71.
25. Banwell B, Tenembaum S, Lennon VA, Ursell E, Kennedy J, Bar-Or A, Weinshenker BG, Lucchinetti CF, Pittock SJ. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. Neurology. 2008;70:344-52.
26. Meinck HM, Thompson PD. Stiff man syndrome and related conditions. Mov Disord 2002;17: 853-66.
27. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291-2.
28. Mas N, Saiz A, Leite MI, Waters P, Baron M, Castaño D, Sabater L, Vincent A, Graus F. Anti-Glycine-receptor encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 2011;82:1399-401.
29. Clerinx K, Breban T, Schrooten M, Leite MI, Vincent A, Verschakelen J, Tousseyn To, Vandenberghe W. Progressive encephalomyelitis with rigidity and myoclonus (PERM): resolution after thymectomy. Neurology. 2011;76:303-4
30. Pröbstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011;77: 580-8.
31. Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, Palace J and Vincent A. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology in press 2012.
32. Turner M, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: Glycine and NMDA receptor antibodies. Neurology. 2011;77:439-43.
33. Granerod J, Ambrose HE, Davies NW, et al; on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835-44.
34. Becker EB, Zuliani L, Pettingill R, et al. Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. J Neurol Neurosurg Psychiatry. 2012;83:437-40.

S a ž e t a k

AUTOANTITIJELA KOD ENCEFALOPATIJA

A. Vincent

Nekoliko se postignuća bilježi u utvrđivanju antitijelima posredovanih bolesti središnjega živčanog sustava. Ta se postignuća odnose na prisutnost antitijela u površinskim neuronskim bjelančevinama ili bjelančevinama glijalnih stanica, poglavito ionskih kanala, receptorima i pridruženim bjelančevinama. Iako su prvo opisane kod odraslih osoba, sad ih se može utvrditi i kod djece svih dobnih skupina. Ova je stanja važno prepoznati, jer ona često odgovaraju na imunoterapije.

Deskriptori: AUTOANTITIJELA; DJECA; SREDIŠNJI ŽIVČANI SUSTAV

Primljeno/Received: 30. 3. 2012.
Prihvaćeno/Accepted: 11. 4. 2012.