National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[D] Antibody testing in epilepsy

NICE guideline number tbc

Evidence reviews underpinning recommendation 1.5.1

November 2021

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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ISBN:

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Antibody testing in epilepsy

Review question

In people with epilepsy, who should have antibody testing?

Introduction

Antibodies are proteins produced by the immune system to fight disease, but sometimes the body produces antibodies against itself. In some people presenting acutely with epileptic seizures, and other features of acute encephalopathy, antibodies to brain proteins have been detected. In some cases, these antibodies may be responsible for brain dysfunction and respond to immunosuppressive therapy. In order to determine who might benefit from such treatment, it is necessary to identify the clinical features of patients who should be tested for such antibodies. The aim of this review is to determine in which population of patients antibody testing should be performed.

Summary of the protocol

See Table 1 for a summary of the Population, Index, Presence or absence of a prognostic, risk or predictive factor and Outcome (PPO) characteristics of this review.

Table 1: Summary of the protocol (PPO table)

Population	Children, young people and adults with confirmed epilepsy
Presence or absence of a prognostic, risk or predictive factor	• Age • Behavioural change (sleep disturbance) • Cognitive impairment • History of febrile seizures • MRI hippocampal abnormalities • Neurological abnormalities • Presence of encephalopathy • Presence of other autoimmune disease • Psychiatric or psychological disorder • Seizure type • Status epilepticus *Univariate studies will only be included if no studies with multivariate analysis are identified*
Outcomes	**Critical** • Risk of testing positive for having an antibody (association data, adjusted from regression analyses or similar) • Proportion of those tested with a positive antibody test

OR: odds ratio

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Fifteen studies were included in this review, 10 prospective cohort studies (Atmaca 2017, Errichiello 2009, Falip 2012, Ganor 2005, Gozubatik-Celik 2017, Liimatainen 2010, Niehusmann 2009, Tecellioglu 2018, Tekturk 2018 and Veri 2013), 3 prospective case control studies (Borusiak 2016, Ceyhan Dirican 2016 and Verrotti 2003), 1 retrospective cohort study (Wright 2016) and 1 retrospective case control study (Majoie 2006). All studies reported data on the proportion of positive antibodies identified through testing.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Cases	Controls	Potential risk factors examined
Atmaca 2017 Prospective cohort study Turkey	N=22 people with status epilepticus of unidentified origin	N= 80 n=30 age and sex matched healthy volunteers n=50 patients with relapsing-remitting multiple sclerosis (RRMS)	• History of febrile seizure • Psychiatric or psychological disorder • MRI abnormalities • Status epilepticus
Borusiak 2016 Multi-centre prospective case control study Germany	N=124 people with focal epilepsy and no signs of encephalitis	Not relevant	• None reported
Ceyhan Dirican 2016 Prospective case-control study Turkey	N=26 people with treatment resistant Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS)	N=26 healthy volunteers	• None reported

Study	Cases	Controls	Potential risk factors examined
Errichiello 2009 Prospective cohort study Italy	N=233 people with focal and generalized epileptic	Not relevant	• Presence of other autoimmune disease
Falip 2012 Prospective cohort study Spain	N=42 people with temporal lobe epilepsy	Not relevant	• None reported
Ganor 2005 Prospective cohort study Israel	N=82 people with epilepsy	N=49 n=22 non-neurological health problems n=27 healthy individuals	• History of febrile convulsions • Seizure type (acute and intractable seizures)
Gozubatik-Celik 2017 Prospective cohort study Turkey	N=94 people with focal seizures of unknown cause	N=50 age-and-gender matched healthy individuals.	• History of febrile convulsion • History of inflammatory/ autoimmune disease • Presence of other autoimmune disease • MRI abnormalities
Liimatainen 2010 Prospective cohort study Finland	N= 253 people with focal epilepsy and idiopathic generalised epilepsy	N=200 non-diabetic organ donors	• Presence of other autoimmune disease
Majoie 2006 Retrospective case control study Netherlands	N=106 females with epilepsy	N= 150 n=50 with multiple sclerosis n=62 with stroke n=19 with other neurological diseases n=19 healthy individuals	• Cognitive impairment • Presence of other autoimmune disease • Seizure type
Niehusmann 2009 Prospective cohort study Germany	N=19 females with unexplained new onset epilepsy	N=72 n=61 with cryptogenic epilepsies n=11 with surgically treated epilepsy	• Psychiatric or psychological disorder • Neurological abnormalities • MRI abnormalities

Study	Cases	Controls	Potential risk factors examined
Tecellioglu 2018 Prospective cohort study Turkey	N=77 people with drug resistant epilepsy of unknown cause	Not relevant	• Psychiatric or psychological disorder • MRI abnormalities • Seizure type
Tekturk 2018 Prospective cohort study Turkey	N=50 people with epileptic encephalopathy of unknown cause	N=40 age-and-gender matched healthy volunteers	• History of febrile seizure • Seizure type • MRI abnormalities • Presence of other autoimmune disease • Status epilepticus
Veri 2013 Prospective cohort study Estonia	N=208 children with newly diagnosed epilepsy	N=128 children with functional urinary and gastrointestinal disorders	• Presence of other autoimmune disease • MRI abnormalities
Verrotti 2003 Prospective case control study Italy	N=74 children with controlled and uncontrolled epilepsy	N=50 age-and-gender matched healthy children	• None reported
Wright 2016 Multi-centre retrospective cohort study Netherlands	N=178 children with epilepsy with and without encephalitis	N=112 age-and-gender matched sibling donors of bone marrow transplantation	• Cognitive impairment • History of febrile seizure • Neurological abnormalities • Status epilepticus

CNS: Central Nervous system; GADA: Glutamic acid decarboxylase autoantibodies; TLE: Temporal lope epilepsy; MRI: Magnetic resonance imaging;

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

- Very low quality evidence showed that the overall proportion of positive antibody tests for glutamate/NMDA in people with epilepsy (all seizure types) was 18%. The overall proportion of positive antibody tests for anti-dsDNA Ab's in people with epilepsy (all seizure types) was 16%.

  The proportion of positive antibody tests recorded by all studies according to antibody found were as follows:
  - People with status epilepticus of unidentified origin: 22.7% with NMDA-R, GLY-R, and/ or GABAAR
  - People with focal epilepsy with no sign of encephalitis: 4% with GAD65 and/ or VGKC

  - People with treatment resistant Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS) and mostly easy to treat juvenile myoclonic epilepsy (JME): 6% with GADA
  - People with focal and generalized epilepsy: 3% with GAD65
  - People with temporal lobe epilepsy (TLE) of known and unknown aetiology: 12% with GADA
  - People with partial epilepsy (generalised epilepsy and infantile spasm): 21% with glutamate/AMPA receptor sub-type 3
  - People with partial epilepsy (generalised epilepsy and infantile spasm): 18% with glutamate/NMDA receptor subunit 2A
  - People with focal seizures of unknown cause: 14% with AMPA-R, Anti-CASPR-2, Anti-GABAB-R, Anti-LGI1, GAD, NMDA-R, and/ or VGKC-complex
  - People with focal epilepsy and idiopathic generalised epilepsy: 6% with GADA, or GADA and TPO
  - Female people with epilepsy: 7% with VGKC, or VGKC and GADA
  - People with unexplained new onset epilepsy: 26% with NMDAR
  - People with drug resistant epilepsy of unknown cause: 22% with VGKC and antinuclear antibodies, VGKC and TPO, TPO, VGKC, GAD, or Intracellular antigens (Yo and MA2/TA)
  - People with epileptic encephalopathy of unknown cause: 14% with NMDAR, GABAAR, CASPR2, GAD, and/ or GLYR
  - People with newly diagnosed epilepsy: 7% with GAD65
  - People with controlled and uncontrolled epilepsy: 27% with acL
  - People with controlled and uncontrolled epilepsy: 30% with ANA
  - People with controlled and uncontrolled epilepsy: 5% with GAD
  - People with epilepsy with and without encephalitis: 10% with VGKC-complex, NMDAR, CASPR2, and/ or Contactin-2

- Very low quality evidence showed that the proportion of positive antibody tests in people with cognitive impairment/ developmental delay at intake was 21%.

  The antibodies found in this subgroup were VGKC, GAD, NMDAR, AMPAR, LGI1, CASPR2, and/ or Contactin-2.

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with a history of febrile seizures were as follows:
  - People with a history of febrile seizures and status epilepticus of unidentified origin: 20%
  - People with a history of febrile seizures and confirmed epilepsy: 8%
  - People with a history of febrile seizures and epileptic encephalitis: 33%
  - Children with a history of febrile seizures: 3%

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with pre-existing neurologic signs/ abnormal examinations was 15%.

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with inflammatory/ autoimmune events was 23%.

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with psychiatric/ psychological disorders was 25%.

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with MRI abnormalities were as follows:
  - People with MRI abnormalities: 27%
  - People with MRI abnormalities: 20%
  - People with white matter lesions: 25%
  - People with hippocampal sclerosis: 0%

- Very low quality evidence showed that the proportion of positive antibody tests for GluR3B Ab's according to epilepsy/ seizure type were as follows:
  - People with partial epilepsy: 18%
  - People with generalised epilepsy: 40%
  - People with infantile spasms: 0%

- Very low quality evidence showed that the proportion of positive antibody tests for Glutamate/NMDA according to epilepsy/ seizure type were as follows:
  - People with partial epilepsy: 27%
  - People with generalised epilepsy: 5%
  - People with infantile spasms: 0%

- Very low quality evidence showed that the proportion of positive antibody tests for anti-dsDNA Ab's according to epilepsy/ seizure type were as follows:
  - People with partial epilepsy: 12%
  - People with generalised epilepsy: 30%
  - People with infantile spasms: 10%
  - People with multifocal focus epilepsy: 12%

- Very low quality evidence showed that the proportion of positive antibody tests for any antibody in people with a history of status epilepticus were as follows:
  - People with convulsive status epilepticus: 25%
  - People with non-convulsive status epilepticus: 33%
  - People with epilepsia partialis continua: 0%
  - People with a history of status epilepticus: 0%
  - People with status epilepticus as a presenting feature: 2%

Quality assessment of studies included in the evidence review

See the evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Summary of studies included in the economic evidence review

No studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the risk of testing positive for antibodies and the proportion of those returning a positive result should be included as critical outcomes for this review question. The committee agreed that these two outcomes would help to determine the yield of antibodies in people with epilepsy and enable the committee to make recommendations on who would benefit from antibody testing.

The quality of the evidence

The quality of the evidence was assessed with a modified GRADE approach, using the same principles of GRADE for assessing the quality of the evidence, but a different form of presentation as GRADE is not yet available for single-arm prevalence studies. The evidence was rated as very low, with outcomes downgraded due to low quality rating at the phase of investigation, risk of bias due to study limitations, indirectness of some of the outcomes and risk of publication bias.

The studies contributing evidence to the outcomes did not report evidence from multivariate regression analysis to determine independent associations between the risk factors and positive antibody testing. The studies were assessed with QUIPS checklist and were rated as low quality. Common issues associated with the qualities of the studies include lack of adjustment for confounders (this is, presence of an underlying autoimmune disease) and uncertainty about the adequacy of the statistical models.

There was also indirectness in the evidence contributing to cognitive impairment, history of febrile seizure, psychiatric or psychological disorder, neurological abnormalities, seizure types and status epilepticus. The reasons for the indirectness of the outcomes is the inclusion of antinuclear antibody in 1 study (Tecellioglu 2018) and antibody to contactin-2 in another study (Wright 2016) as part of the reported proportion of those positive for antibody in the evidence from 2 studies. These antibodies were outside of the scope of the protocol for this review. One of the studies (Ganor 2005) also reported the identified risk factors among people with epilepsy with a single type of antibody without reporting the risk factors for those with multiple types of antibody.

Benefits and harms

Considering the low quality and limited evidence available the committee decided that antibody testing in epilepsy is an area that requires further research. The committee agreed it

would be useful to make a research recommendation to determine the pathophysiological implications of the presence of autoimmune autoantibodies in epilepsy (see Appendix L).

The committee further noted that the heterogeneity in the data presented could have been due to different classification criteria being used across the studies, thereby making the outcomes difficult to interpret. Hence, the committee recommended that further research should consider using standard classification criteria for patients entering into autoantibody studies.

The committee agreed that the evidence presented was limited, and did not support routine antibody testing in clinical practice for people with epilepsy. The committee acknowledged that at present the number of normal controls who carry these antibodies is unclear, as such it is not possible to determine if the antibodies cause epilepsy, or whether subsequent treatment of the antibodies will improve the epilepsy. The committee agreed that conducting routine antibody testing on people with epilepsy based on unclear evidence carried the risk of over-emphasising the potential significance of the presence of certain antibodies.

However, the committee noted that many people with epilepsy with autoimmune encephalitis may present either with acute seizures or status epilepticus associated with encephalopathy. The committee knew from their knowledge and experience that people with encephalopathy can have better outcomes from immunotherapy than with standard antiseizure medication, and therefore agreed by informal consensus that it could be beneficial to undergo antibody testing in this group.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Routine antibody testing would have led to a significant resource impact compared to current practice. However, the evidence presented did not support such a recommendation. No recommendations were made in this area that would change current practice and consequently have a resource impact.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.1 and the research recommendation on immunomodulation strategies.

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Atmaca, M. M., Tuzun, E., Erdag, E., Bebek, N., Baykan, B., Gurses, C., Investigation of anti-neuronal antibodies in status epilepticus of unknown etiology: a prospective study, Acta Neurologica Belgica, 117, 841-848, 2017

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Appendices

Appendix A – Review protocol

Review protocol for review question: In people with epilepsy, who should have antibody testing?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42019151512
Review title	Antibody testing in epilepsy
Review question	In people with epilepsy, who should have antibody testing?
Objective	The objective of this review is to determine in which population of patients antibody testing should be performed. The committee agreed that a positive antibody test is of benefit as this means the patient can be given appropriate autoimmune therapy. The aim is to identify which factors of an individual are associated with a positive antibody test, this is, when a person presents in clinic, what characteristics should that person have which means having an antibody test is a productive option, rather than simply testing everybody.
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by: • Date: 1995 onwards (date when antibody testing was first introduced) • English language studies • Human studies

Field	Content
	The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Epilepsy
Population	Inclusion: Children, young people and adults with confirmed epilepsy (individuals may be at any stage, this is they may have received MRI, or metabolic testing). Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
Test	Any epilepsy related antibody test, including: • AMPA 1 • AMPA 2 • Autoantibodies directed against glutamic acid decarboxylase (GAD) • Contactin-associated protein-like 2 (CASPR2) • GABA A • GABA B • Glycine receptors • Intracellular antigens (Hu, Ma2, Amphiphysin, Ri, CRMP5 and Yo) • neuronal cell surface antigens (such as N-methyl-D-aspartate receptor (NMDAR) • Thyroid Peroxidase (TPO) • voltage gated potassium channel (VGKC)-complexes (leucine-rich glioma-inactivated protein 1 [LGI1])
Risk factors	• Age • Behavioural change (sleep disturbance) • Cognitive impairment • History of febrile seizures • MRI hippocampal abnormalities • Neurological abnormalities • Presence of encephalopathy • Presence of other autoimmune disease • Psychiatric or psychological disorder • Seizure type

Field	Content
	• Status epilepticus
Types of study to be included	• Multivariate regression analysis • Cross sectional studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies in cohort of known size Univariate case control studies • Non-nested case control studies • Cross-sectional studies Univariate studies will only be included if no studies with multivariate analysis are identified. Studies will only be included if all participants have received antibody testing Conference abstracts will not be included.
Other exclusion criteria	Studies with a mixed population (this is, including children, young people and adults with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported. Studies with univariate regression analysis will be included only if there are no studies that use multivariate regression analysis ,
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care).
Primary outcomes (critical outcomes)	• Risk of testing positive for having an antibody (association data, adjusted from regression analyses or similar) • Proportion of those tested with a positive antibody test
Secondary outcomes (important outcomes)	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

Field	Content
	Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • QUIPS checklist for prognostic factor studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	<u>Synthesis of data:</u> • Odds Ratios will be extracted for each risk factor listed. • The clinical characteristic will where possible will be categorised, this is, those children above 3 years (positive) and those below 3 years (negative). • Meta-analysis to combine the effect estimates (OR) across studies for an independent prognostic factor will be conducted only if there is sufficient number of studies, a consistent measure to assess this factor is used, and each study has adjusted for similar sets of confounders. Otherwise a narrative summary of the available results for each factor will be provided. <u>Heterogeneity:</u> • Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted. Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. <u>Appraisal of quality of evidence:</u> • The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/"

Field	Content			
Analysis of sub-groups	Analysis will be conducted separately for adults and children			
Type and method of review	☐	Intervention		
	☐	Diagnostic		
	☒	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	30 July 2019			
Anticipated completion date	07 April 2021			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		x	x
	Piloting of the study selection process		x	x
	Formal screening of search results against eligibility criteria		x	x
	Data extraction		x	x
	Risk of bias (quality) assessment		x	x
	Data analysis		x	x
Named contact	5a. Named contact National Guideline Alliance 5b. Named contact e-mail epilepsies@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance			
Review team members	National Guideline Alliance (NGA) technical team			
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE and hosted by the Royal College of Obstetricians and Gynaecologists.			

Field	Content	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112	
Other registration details	Not applicable	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019151512	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Epilepsy, Antibody testing, Children	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: In people with epilepsy, who should have antibody testing?

Clinical

Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID

EMCare 1995 to 2019 June 21; Embase Classic+Embase 1947 to 2019 June 21; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2019 June 21, 2019

Date of last search: 21 June 2019

Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp epilepsy/ or landau kleffner syndrome/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd, emcr
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(convulsion* or dravet syndrome or epilep* or continous spike wave of slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6	or/2,4-5
7	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
8	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
9	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
10	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or smei or lennox gastaut or lgs or (landau adj2 kleffner)).ti,ab.
11	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
12	or/6-11
13	autoantibodies/ use emczd, emcr,ppez
14	(autoantibod* or auto antibod*).ti,ab.

#	Searches
15	or/13-14
16	antibody/ use emczd, emcr or antibodies/ use ppez
17	antibod*.ti,ab.
18	or/16-17
19	((((autoantibodies adj3 against glutamic acid decarboxylase) or gad or gad-ab or gadab* or gad 65* or gad65*) and gad67*) or gad 67*).ti,ab.
20	(contactin-associated protein-like 2 or caspr2 or caspr 2).ti,ab.
21	exp voltage gated potassium channel/ use emczd, emcr or exp potassium channels, voltage-gated/ use ppez
22	(voltage gated potassium channel* or vgkc*1).ti,ab.
23	potassium channel*.ti,ab.
24	(kva1* or kva2* or kva2* or kva3* or kva4* or kva5* or kva6* or kva7* or kva8* or kva9* or kva10* or kva11* or kva12* or kv1* or kv2* or kv3* or kv4* or kv5* or kv6* or kv7* or kv8* or kv9* or kv10* or kv11* or kv12* or kcna1 or kcna10 or kcna2 or kcna3 or kcna4 or kcna5 or kcna6 or kcna7 or kcnb1 or kcnb2 or kcnc1 or kcnc2 or kcnc3 or kcnc4 or kcnd1 or kcnd2 or kcnd3 or kcnf1 or kcng1 or kcng2 or kcng3 or kcng4 or kcnh1 or kcnh2 or kcnh3 or kcnh4 or kcnh5 or kcnh6 or kcnh7 or kcnh8 or kcnq1 or kcnq2 or kcnq3 or kcnq4 or kcnq5 or kcns1 or kcns2 or kcns3 or kcnv1 or kcnv2 or kcnip1 or kcnip2 or kcnip3 or kcnip4 or kcnab1 or kcnab2 or kcnab3 or kcne1 or mirp1 or kcne2 or mirp2 or kcne3 or mirp3 or kcne4 or kcne1l).ti,ab.
25	(leucine-rich glioma-inactivated 1 or leucine-rich glioma-inactivated protein 1 or lgi1).ti,ab.
26	or/21-25
27	thyroid peroxidase/ use emczd, emcr or iodide peroxidase/ use ppez
28	(thyroid gland peroxidase or thyroid peroxidase or thyroperoxidase or tpo).ti,ab.
29	or/27-28
30	receptors, gaba-b/ use ppez or gamma-aminobutyric acid/ use ppez or 4 aminobutyric acid a receptor/ use emczd, emcr
31	(aminobutyric acid or baclofen receptor* or gaba a or gabaa or gabaar or gabab or gaba b or gab-abr).ti,ab.
32	or/30-31
33	ampa receptor/ use emczd, emcr or receptors, ampa/ use ppez
34	((ampa adj2 receptor*) or ampa 1 or ampa 2 or ((excitatory amino or quisqual* acid or quisqual*) adj receptor*)).ti,ab.
35	or/33-34
36	n methyl dextro aspartic acid receptor/ use emczd, emcr or receptors, n-methyl-d-aspartate/ use ppez
37	(neuronal cell surface antigen* or (n methyl d adj (aspartate or aspartic acid) adj receptor*) or nmdar or nmda receptor).ti,ab.
38	or/36-37
39	glycine receptor/ use emczd, emcr or receptors, glycine/ use ppez
40	(glycin* adj (nerve cell or receptor*)).ti,ab.
41	or/39-40
42	antigen/ or nucleolysin tia 1 isoform p40/ or hu antibody/ or amphiphysin/

#	Searches
43	42 use emczd, emcr
44	t-cell intracellular antigen-1/ use ppez
45	antigen*.ti,ab.
46	(collapsin response mediator protein 5 or crmp5 or crmp 5).ti,ab.
47	amphiphysin.ti,ab.
48	(human antigen r or hur or (hu and (antigen* or antibod* or autoantibod*))).ti,ab.
49	(paraneoplastic antigen or pnma2 or pnma 2 or ma2 or ma 2 or (ma and (antigen* or antibod* or auto-antibod*))).ti,ab.
50	((ri or nova or nova1 or anna 2 or anna2) and (antigen* or antibod* or autoantibod*)).ti,ab.
51	(crd2 or (yo and (antigen* or antibod* or autoantibod*))).ti,ab.
52	or/41,43-51
53	or/15,18-20,26,29,32,35,38,52
54	predict.ti.
55	(validat* or rule*).ti,ab.
56	(predict* and (outcome* or risk* or model*)).ti,ab.
57	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
58	logistic models/ use ppez or statistical model/ use emczd, emcr
59	58 and decision*.ti,ab.
60	(decision* and (model* or clinical*)).ti,ab.
61	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
62	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
63	roc curve/ use ppez or receiver operating characteristic/ use emczd, emcr
64	or/54-57,59-63
65	"*area under the curve"/ or *diagnostic accuracy/ or exp diagnostic test/ or diagnostic test accuracy study/ or *predictive validity/ or *receiver operating characteristic/ or *reliability/ or "*sensitivity and specificity"/ or statistical model/ or *test retest reliability/ or *validity/ or diagnos*.sh. or di.fs.
66	65 use emczd, emcr
67	"area under curve"/ or diagnostic tests, routine/ or likelihood functions/ or "predictive value of tests"/ or "reproducibility of results"/ or roc curve/ or "sensitivity and specificity"/ or validation studies/ or diagnos*.sh. or di.fs.
68	67 use ppez
69	(accurac* or accurat* or area under curve or auc or clinical utilit* or (diagnos* adj2 (accurac* or analys* or effectiveness or efficien* or odds ratio or performance* or screen* or sequenc* or test* or utilit* or value*)) or (likelihood adj3 ratio*) or npv or ((pretest or pre test or posttest or post test) adj2 probabilit*) or (predict* adj3 value*) or ppv or receiver operating characteristic or (roc adj2 curv*) or reliabil* or sensititiv* or specificit* or valid*).tw. or diagnos*.ti. or gold standard.ab.
70	or/66,68-69

#	Searches
71	or/64,70
72	12 and 53 and 71
73	limit 72 to english language
74	limit 73 to yr="1995 -current"
75	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
76	75 use emez
77	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)
78	77 use mesz
79	76 or 78
80	74 not 79

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 6 of 12, June 2019; Cochrane Central Register of Controlled Trials, Issue 6 of 12, June 2019

Date of last search: 21 June 2019

#	searches
1	mesh descriptor: [epilepsy] explode all trees
2	mesh descriptor: [seizures] this term only
3	mesh descriptor: [seizures, febrile] this term only
4	mesh descriptor: [status epilepticus] explode all trees
5	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep“ or “landau kleffner syndrome” or ”lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”):ti,ab
6	(((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in* flexion or spasmus nutans or west syndrome*):ti,ab
7	((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy) or ((absence or astatic or atonic or tonic or tonic clonic) near/2 (seizure* or spasm*)):ti,ab
8	(bcects or bects or brec or benign epilepsy or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab
9	(dravet or lennox gastaut or lgs or (landau near/2 kleffner) or smei) :ti,ab

#	searches
10	(dravet* or (intractable childhood epilepsy near/2 (generalised tonic clonic or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei) :ti,ab
11	{or #1-#10}
12	mesh descriptor: [autoantibodies] this term only
13	mesh descriptor: [antibodies] this term only
14	mesh descriptor: [potassium channels, voltage-gated] explode all trees
15	mesh descriptor: [iodide peroxidase] this term only
16	mesh descriptor: [receptors, gaba-b] this term only
17	mesh descriptor: [gamma-aminobutyric acid] this term only
18	mesh descriptor: [receptors, ampa] this term only
19	mesh descriptor: [receptors, n-methyl-d-aspartate] this term only
20	mesh descriptor: [receptors, glycine] this term only
21	mesh descriptor: [t-cell intracellular antigen-1] this term only
22	(autoantibod* or auto antibod*):ti,ab
23	antibod*:ti,ab
24	((((autoantibodies near/3 against glutamic acid decarboxylase) or gad or gad-ab or gadab* or gad 65* or gad65*) and gad67*) or gad 67*):ti,ab
25	(contactin-associated protein-like 2 or caspr2 or caspr 2) :ti,ab
26	(voltage gated potassium channel* or vgkc*):ti,ab
27	“potassium channel*”:ti,ab
28	(kva1* or kva2* or kva2* or kva3* or kva4* or kva5* or kva6* or kva7* or kva8* or kva9* or kva10* or kva11* or kva12* or kv1* or kv2* or kv3* or kv4* or kv5* or kv6* or kv7* or kv8* or kv9* or kv10* or kv11* or kv12* or kcna1 or kcna10 or kcna2 or kcna3 or kcna4 or kcna5 or kcna6 or kcna7 or kcnb1 or kcnb2 or kcnc1 or kcnc2 or kcnc3 or kcnc4 or kcnd1 or kcnd2 or kcnd3 or kcnf1 or kcng1 or kcng2 or kcng3 or kcng4 or kcnh1 or kcnh2 or kcnh3 or kcnh4 or kcnh5 or kcnh6 or kcnh7 or kcnh8 or kcnq1 or kcnq2 or kcnq3 or kcnq4 or kcnq5 or kcns1 or kcns2 or kcns3 or kcnv1 or kcnv2 or kcnip1 or kcnip2 or kcnip3 or kcnip4 or kcnab1 or kcnab2 or kcnab3 or kcne1 or mirp1 or kcne2 or mirp2 or kcne3 or mirp3 or kcne4 or kcne1l) :ti,ab
29	(“leucine-rich glioma-inactivated 1” or “leucine-rich glioma-inactivated protein 1” or lgi1) :ti,ab
30	(“thyroid gland peroxidase” or “thyroid peroxidase” or thyroperoxidase or tpo) :ti,ab
31	(“aminobutyric acid” or “baclofen receptor*” or gaba a or gabaa or gabaar or gabab or gaba b or gababr) :ti,ab
32	((ampa near/2 receptor*) or ampa 1 or ampa 2 or ((“excitatory amino” or quisqual* acid or quisqual*) next receptor*)):ti,ab
33	(“neuronal cell surface antigen*” or (“n methyl d” next (aspartate or “aspartic acid”) next receptor*) or nmdar or “nmda receptor”) :ti,ab
34	(glycin* next (nerve cell or receptor*)):ti,ab
35	antigen*:ti,ab
36	(“collapsin response mediator protein 5” or crmp5 or “crmp 5”) :ti,ab
37	Amphiphysin:ti,ab

#	searches
38	("human antigen r" or hur or (hu and (antigen* or antibod* or autoantibod*))):ti,ab
39	("paraneoplastic antigen" or pnma2 or "pnma 2" or ma2 or "ma 2" or (ma and (antigen* or antibod* or autoantibod*))):ti,ab
40	((ri or nova or nova1 or anna 2 or anna2) and (antigen* or antibod* or autoantibod*)):ti,ab
41	(crd2 or (yo and (antigen* or antibod* or autoantibod*))):ti,ab
42	{or #12-#41}
43	predict.ti.
44	(validat* or rule*):ti,ab
45	(predict* and (outcome* or risk* or model*)):ti,ab
46	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)):ti,ab
47	mesh descriptor: [logistic models] this term only
48	#47 and decision*:ti,ab
49	(decision* and (model* or clinical*)):ti,ab
50	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)):ti,ab
51	(stratification or discrimination or discriminate or "c statistic" or "area under the curve" or auc or calibration or indices or algorithm or multivariable) :ti,ab
52	mesh descriptor: [roc curve] this term only
53	{or #43-#46,#48-#52}
54	("area under curve" or "diagnostic tests, routine" or "likelihood functions" or "predictive value of tests" or "reproducibility of results" or "roc curve" or "sensitivity and specificity" or "validation studies" or diagnos*):kw
55	(accurac* or accurat* or "area under curve" or auc or clinical utilit* or (diagnos* near/2 (accurac* or analys* or effectiveness or efficien* or "odds ratio" or performance* or screen* or sequenc* or test* or utilit* or value*)) or (likelihood near/3 ratio*) or npv or ((pretest or "pre test" or posttest or "post test") near/2 probabilit*) or (predict* near/3 value*) or ppv or "receiver operating characteristic" or (roc near/2 curv*) or reliabil* or sensititiv* or specificit* or valid*):ti,ab or diagnos*:ti. or "gold standard":ab
56	{or #54- #55}
57	#53 or #56
58	#11 and #42 and #57 with Cochrane Library publication date from Jan 1995 to June 2019

Database(s): DARE; HTA database - CRD

Date of last search: 21 June 2019

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees

#	searches
5	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”)
6	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)
7	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or tonic clonic) near2 (seizure* or spasm*))
8	(bcects or bects or brec or “benign epilepsy” or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
9	(dravet or “lennox gastaut” or lgs or (landau near2 kleffner) or smei)
10	(dravet* or (“intractable childhood epilepsy” near2 (generalised tonic clonic or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
11	{or #1-#10}

Economic

Database(s): MEDLINE & Embase (Multifile) - OVID
Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021
Date of last search: 31 March 2021

Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab.
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab.
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora

#	searches
	body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD

Date of last search: 31 March 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”)
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or “petit mal*” or pyknolepsy or “typical absence*”)
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or “brief seizure” or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only

#	searches
10	(bcects or bects or brec or "benign epilepsy" or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or "temporal-central focal") near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or "myoclonic astatic" or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 "eyelid myoclonia") or (ige near2 phantom absenc*) or "impulsive petit mal" or (janz near3 (epilep* or "petit mal")) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or "perioral myoclon*")
13	mesh descriptor spasms, infantile this term only
14	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal"or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or "lennox gastaut" or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	("child* epileptic encephalopath*" or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or "progressive familial epilep*" or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or "muscle jerk")
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or "doose* syndrome" or mae or "generali?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or "focal onset" or local or partial or "simple partial") near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or "grand mal" or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

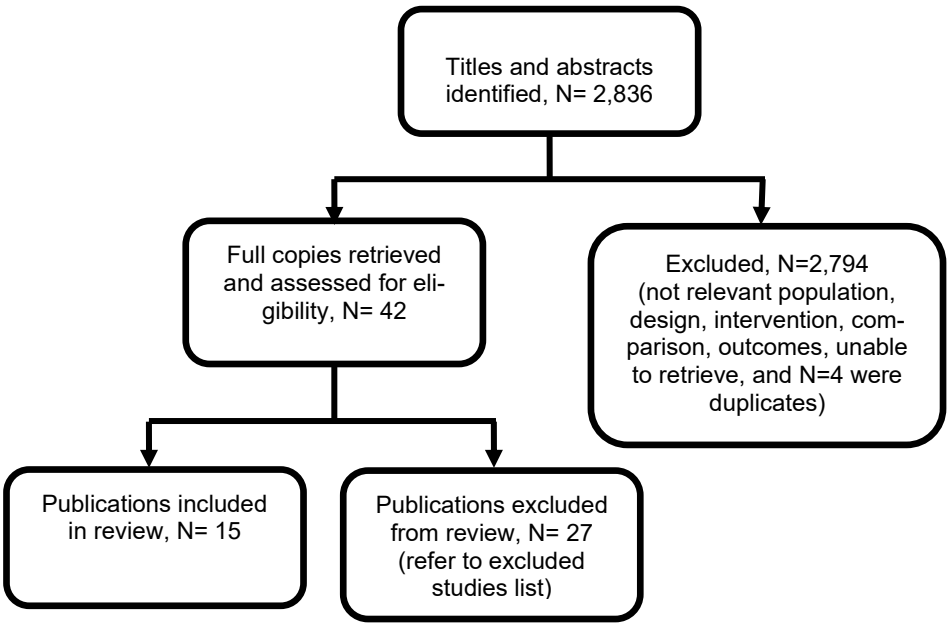
1

2

Appendix C – Clinical evidence study selection

Study selection for: In people with epilepsy, who should have antibody testing?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: In people with epilepsy, who should have antibody testing?

Table 4: Evidence tables

Study details	Participants	Factors	Results	Comments
Full citation Atmaca, M. M., Tuzun, E., Erdag, E., Bebek, N., Baykan, B., Gurses, C., Investigation of anti-neuronal antibodies in status epilepticus of unknown etiology: a prospective study, Acta Neurologica Belgica, 117, 841-848, 2017 **Ref Id** 1068492 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Study dates**	**Cases** 22 adults with status epilepticus of unknown aetiology. **Diagnostic criteria** ILAE classification **Controls** 80 **Inclusion criteria** • Cases were patients with status epilepticus (SE) with unidentified etiology. • Control were age and sex match health volunteers and patients with relapsing-remitting multiple sclerosis (RRMS) **Exclusion criteria** • Patients with status epilepticus (SE) with identified etiology.	**Factors** Status epilepticus was defined according to the classification of the International League Against Epilepsy (ILAE) Risk factors: Seronegative and seropositive patients were compared in terms of: • age • history of febrile convulsion • presence of psychiatric diseases • MRI abnormalities • Status epilepticus type Antibodies tested for: • VGKC (normal values <50pm) • CASPR-2 • LGI1 • GAD (normal values 10<U/ml) • NMDA-R • GLY-R	**Results** Proportion of positive antibody tests (any) – all patients N=5/22 NMDA-R n=2/22; Gly-R n=2/22; GABA(A)R n= 1/22 No antibodies were identified against CASPR-2, LGI1, uncharacterized VGKC-complex antigens, or AMPA-R or GABABR. Proportion of positive antibody tests (any) in patients with convulsive status epilepticus n=3/12 Proportion of positive antibody tests (any) in patients with non-convulsive status epilepticus n=2/6 Proportion of positive antibody tests (any) in patients with epilepsia partialis continua n=0/4	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if measurement is valid and reliable for all participants and unsure if method and setting of measurement is the same for all participants may likely introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure if statistical model is adequate, no regression model presented, may likely introduce substantial bias) **Overall Quality: Low**

Study details	Participants	Factors	Results	Comments
February 2012-December 2013 **Consecutive recruitment** Yes **Funding** • Atmaca received grant from the Istanbul University Scientific Research Projects. • Baykan received grant from the Turkish Scientific and Technical Research Council.	**Statistical method** Descriptive statistics were applied, and the 2 groups of patients with and without serum antibodies were compared using the X^2 test, Fisher's exact test, and independent samples t test, where appropriate. SPSS 18 was used and the significance level was set at $p<0.05$. **Demographics** Cases: N= 22 (adult patients with SE of unidentified origin). Control: N=80 (30 age and sex matched healthy volunteers and 50 patients with RRMS) Age (years), range; mean ± SD: Cases only: 17-90; 48.4 ±23 years Gender, number Cases only: • Female: N= 18 • Male: N= 4	• AMPA-R • $GABA_AR$ • $GABA_BR$. • Hu, Yo, Ri, Ma2, Amphiphysin were investigated in cases with an accompanying systemic cancer.	Proportion of positive antibody tests (any) in patients with febrile seizures n=1/5 Proportion of positive antibody tests (any) in patients with psychiatric disorders n=1/4 Proportion of positive antibody tests (any) in patients with MRI abnormalities n=3/11	
Full citation Borusiak, P., Bettendorf, U., Wiegand, G.,	**Cases** 124 children with focal epilepsy > 1 year and < 18	**Factors** Seizures and Epilepsies were classified according to	**Results** Proportion of epilepsy patients with positive antibody test – any	**Limitations** QUIPS Checklist: Risk of Bias Assessment

Study details	Participants	Factors	Results	Comments
Bast, T., Kluger, G., Philippi, H., Munstermann, D., Bien, C. G., Autoantibodies to neuronal antigens in children with focal epilepsy and no prima facie signs of encephalitis, European Journal of Paediatric Neurology, 20, 573-579, 2016 **Ref Id** 1067743 **Country/ies where the study was carried out** Germany **Study type** Multi-centre prospective case control study **Study dates** April 2011-May 2014 **Consecutive recruitment** Yes **Funding**	years.Two different groups were recruited depending on the course of epilepsy of last six months irrespective of autoantibodies which were analyzed en bloc at the end of the study. The patients were classified before the antibody analysis was done in terms of epilepsy type and treatability. We did not intend to include all patients with epilepsy at the participating centers but rather to create two distinctive groups: well controlled epilepsies compared to a cohort of difficult to treat epilepsies. In order to avoid any overlap the first group consisted of patients without severe problems concerning seizure control ("easy to treat group", group 1). **Diagnostic criteria** ILAE classification **Controls** **Inclusion criteria** • Easy to treat group of patients: a maximum of 1 seizure during last 6	the classification of the International League against Epilepsy (ILAE). Antibodies tested for: • GAD65-(High titre ≥500) • NMDAR • $GABA_BR$ • AMPA1/2-R • Glycin-receptor • LGI1 • CASPR-2 • VGKC-(positive values >100pmol/l) • Amphiphysin, CV2.1/CRMP5, Ma2, Hu,Ri, Yo	N=5/124 (difficult to treat: n=2; easy to treat: n=3) Proportion with positive GAD65 test (high-positive 1:64,000) n=1/124 (difficult to treat n=0; easy to treat n=1). Proportion with positive GAD65 test (low-positive 1:100) n=1/124 (difficult to treat n=0; easy to treat n=1). Proportion with positive VGKC not reactive with LGI1 or CASPR-2 test n=3 (142 pmol/l, 147 pmol/l, 223 pmol/l) (difficult to treat: n=2; easy to treat: n=1)	**Study Participation**: Low risk (unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: High risk (no definition was provided for prognostic factors, unsure if method of measurement of prognostic factors was valid and reliable, unsure if method and setting of measure of the factors was the same for all participants, unsure if adequate proportion of the study population had complete data, very likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: High risk (no statistical model presented and unsure if all valid results were presented, very likely to introduce substantial bias) **Overall Quality: Low** **Other information** Note: • No distinguishing risk factor was found • No antibodies were found for the ones not reported under the results section

Study details	Participants	Factors	Results	Comments
Research awards from the German Section of the International League Against Epilepsy, the HELIOS Research Center and Novartis Pharma.	months, a present combination therapy of at most 2 drugs and not more than 3 different drugs for long term treatment in their treatment history. • Additional emergency treatment with diazepam, lorazepam, etc. in the past was accepted. • Patients with difficult to treat epilepsy – persisting seizures: at least 2 persistent seizures during last 6 months despite adequately chosen drugs and treatment with at least 3 different drugs in the past. **Exclusion criteria** • Patients not completely fulfilling the criteria of respective groups (easy or difficult to treat). • Children who either themselves or their parents were not willing to participate. **Statistical method** Not reported. **Demographics**			

Study details	Participants	Factors	Results	Comments
	N=124 children with focal epilepsy and no prima facie signs of encephalitis N=74 difficult to treat patients N=50 easy to treat patients Age (years), mean ± SD: 10.6±4.11years difficult to treat patients: 10.0±4.11 years easy to treat patients: 11.3±4.9 years Sex, number Difficult to treat – female n=33; male n=41 Easy to treat - female: N=29; male: N=21			
Full citation Ceyhan Dirican, A., Elibirlik, S., Koksal, A., Ozturk, M., Altunkaynak, Y., Baybas, S., Dirican, A., Evaluation of glutamic acid decarboxylase antibody levels in patients with juvenile myoclonic epilepsy and mesial temporal lobe epilepsy with hippocampal sclerosis,	**Cases** 54 patients with partial and idiopathic generalised epilepsy (n=28 juvenile myoclonic epilepsy and n=26 mesial temporal lobe epilepsy with hippocampal sclerosis) **Diagnostic criteria** ICEES **Controls**	**Factors** Type of epilepsy was determined according to the International Classification of Epilepsies and Epileptic Syndromes (ICEES). Antibodies tested for: • GAD (positive level cut-off: 1.0 U/ml) • TPO in patients positive for GADA	**Results** Proportion of epilepsy patients with positive antibody test (GADA) n=3/54 (MTLEHS n=1; JME n=2).	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Moderate risk (inadequate description of sampling frame and unsure if there was adequate participation of eligible individuals, may likely introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition was provided for prognostic factors, unsure if measurement was valid and reliable for all participants, unsure if method and setting of

Study details	Participants	Factors	Results	Comments
Noropsikiyatri Arsivi, 53, 253-256, 2016 **Ref Id** 1068508 **Country/ies where the study was carried out** Turkey **Study type** Case-control study **Study dates** June 2010-June 2012 **Consecutive recruitment** Yes **Funding** None	26 age-matched, healthy controls **Inclusion criteria** • Epileptic patients who had been admitted to the Epilepsy Centre at Bakirkoy Psychiatry, Neurology, Neurosurgery Research and Training Hospital from 2010 to June 2012. • Controls were healthy volunteers without any history of neurological or endocrinological diseases. **Exclusion criteria** • Patients who had neurological symptoms such as ataxia, dysmetria, dysdiadochokinesia, rigidity, encephalopathy, and cognitive and/or psychiatric manifestations that are indicative for GADA-associated neurological syndromes. **Statistical method** • GADA levels were compared between groups using the X^2 test. Fisher's exact test			measurement was the same, likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure if statistical model is adequate, no regression model presented and unsure if all valid results were presented, may likely introduce substantial bias) **Overall Quality: Low** **Other information** No distinguishing risk factor was found.

Study details	Participants	Factors	Results	Comments
	and X^2 tests were used for comparing the frequencies, mean values, and standard deviations of the variables. The Kruskal-Wallis test was used to compare the 3 groups for nonparametric variables. P<0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 21.0. **Demographics** N=80 N=26 Treatment resistant Mesial temporal lope epilepsy with hippocampal sclerosis (MTLEHS). N=28 Juvenile Myoclonic epilepsy (JME)-(mostly easy to treat, with N=4 drug resistant patients). Control: N=26 healthy volunteers. Age (years), range, mean ± SD MTLEHS: 18-42, 31.9±6.6 JME: 16-40, 25.3±7.5 Control: 17-43, 28.7±7.3 Age at seizure onset (years), range, mean ± SD			

Study details	Participants	Factors	Results	Comments
	MTLEHS: 5-23, 11.2±4.9 JME: 7-22, 14.8±2.6 Gender, number MTLEHS: female n=15; male n=11 JME: female n=22; male n=6 Control group – female n=16; male n=10.			
Full citation Errichiello, L., Perruolo, G., Pascarella, A., Formisano, P., Minetti, C., Striano, S., Zara, F., Striano, P., Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: A study on 233 patients, Journal of Neuroimmunology, 211, 120-123, 2009 **Ref Id** 1066627 **Country/ies where the study was carried out** Italy **Study type**	**Cases** 233 **Diagnostic criteria** ILAE classifications **Controls** **Inclusion criteria** • Epileptic patients attending the Epilepsy Center at "Federico II" University, Napoli, from April 2006 to April 2008. **Exclusion criteria** • Patients showing additional neurological features (such as ataxia, cerebellar signs, rigidity, encephalopathic course, cognitive and psychiatric manifestations) indica-	**Factors** Epileptic syndromes were classified according to the international League Against Epilepsy. Risk factor • Presence of other autoimmune diseases Antibody tested for: • GAD65 (positive level cut-off point: 0.9 U/ml).	**Results** Proportion of positive antibody tests (GADA) – all patients N=6/233 (cryptogenic focal epilepsy n=4; idiopathic generalised epilepsy (n=2) Proportion of GADA positive patients positive for other antibodies (anti-islet cell-specific, anti-insulin, anti-protein tyrosine phosphataselike protein, anti-cardiolipin, anti-nuclear, anti-thyroid peroxidase, anti-gliadin and anti-GM1 antibodies): n=0/6	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (unsure if measurement was valid and reliable for all participants, unsure if method and setting of measurement was the same, but unlikely to introduce substantial bias). **Outcome Measurement**: Moderate risk (unsure if method and outcome measurement is adequately valid and reliable, blinding of measurement and confirmation of outcome with valid and reliable test was not mentioned, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders)

Study details	Participants	Factors	Results	Comments
Prospective cohort study **Study dates** April 2006-April 2008 **Consecutive recruitment** Yes **Funding** None	tive of other GADA-associated neurological conditions. **Statistical method** • Statistical analysis was performed using Fisher's exact test with Yates' correction. **Demographics** N=233 Patients with GADA: N=6 Focal and generalized epileptic. Patients without GADA: N=227 Focal and generalized epileptic. Age (years), range; mean: 6-78 years; 29.3 years Age at seizure onset (years), range; median: 3-51 years; 22.3 years Gender, number Female: N=121 Male: N=112			**Statistical Analysis and Reporting**: High risk (unsure if statistical model is adequate, no regression model presented and unsure if all valid results were presented, very likely to introduce substantial bias). **Overall Quality: Low**
Full citation Falip, M., Carreno, M., Miro, J., Saiz, A., Villanueva, V., Quilez, A., Molins, A., Barcelo, I., Sierra, A., Graus, F., Prevalence and immunological spectrum of temporal	**Cases** 42 consecutive patients with epilepsy after the age of 30 and with clinical (using seizure semiology) MRI and EEG features of temporal lobe epilepsies, whether associated or not with hippocampal sclerosis,	**Factors** Antibodies tested for: • TPO • GAD • In those patients with positive GAD-ab, HEK293 cells transfected	**Results** Proportion of positive antibody tests GAD-ab – all patients N=5/42 (unknown aetiology n=5). High GAD-ab level: n=2; low GAD-ab level: n=3)	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Moderate risk (epileptic diagnostic criteria was not reported, unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain)

Study details	Participants	Factors	Results	Comments
lobe epilepsy with glutamic acid decarboxylase antibodies, European Journal of Neurology, 19, 827-33, 2012 **Ref Id** 1068540 **Country/ies where the study was carried out** Spain **Study type** Prospective cohort study **Study dates** January 2008-November 2009 **Consecutive recruitment** Yes **Funding** Study was supported in part by a grant from the Spanish National Institute of Health.	**Diagnostic criteria** Not reported **Inclusion criteria** • Patients with epilepsy onset beyond the age of 30 and with clinical (using seizure semiology) MRI and EEG features of temporal lobe epilepsy (TLE), whether associated or not with hippocampal sclerosis (HS), who are attended to in the outpatient epilepsy clinic of Bellvitge Hospital. • Patients whose onset of TLE occurred after age 30 to expand the spectrum of other potential precipitating injuries. (All patients had a minimum period of follow-up since the diagnosis of epilepsy of 2 years) **Exclusion criteria** Not mentioned. **Statistical method** • Fishers exact test was used for nominal data and the Mann–Whitney U-test for metric data. All tests were two-tailed;	with the B_1 and B_2 subunits of $GABA_B$ ($GABA_BR$). • In those patients with positive GAD-ab, onconeuronal antibodies were investigated: Hu, Yo, Ma and amphiphysin.	None of the patients had GABABR antibodies.	**Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if method of measurement is s adequate and valid, unsure if method of measurement is the same for all participants, unsure if adequate proportion of the study population has complete data for prognostic factors, may likely introduce substantial bias). **Outcome Measurement**: Moderate risk (Unsure if method of outcome measurement is adequately valid and reliable, blind measurement and confirmation with valid and reliable test was not mentioned, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: High risk (unsure if statistical model is adequate, no regression model presented and unsure if all valid results were presented, very likely to introduce substantial bias). **Overall Quality: Low** **Other information** Note: • Characteristics of GADA positive patients in the study could not be isolated for reporting. • Results for positive TPO antibodies could not be isolated from the article.

Study details	Participants	Factors	Results	Comments
	P-values < 0.05 were considered significant. **Demographics** N=42 N=23 TLE of unknown aetiology N=19 TLE of known aetiology Age (years), mean± SD: 56.22±2.3 years Age at seizure onset (years), mean±SD: 48.32± 6.8 years Gender, number Female: N=25 Male: N=17			
Full citation Ganor, Y., Goldberg-Stern, H., Lerman-Sagie, T., Teichberg, V. I., Levite, M., Autoimmune epilepsy: Distinct subpopulations of epilepsy patients harbor serum autoantibodies to either glutamate/AMPA receptor GluR3, glutamate/NMDA receptor subunit NR2A or double-stranded DNA, Epilepsy research, 65, 11-22, 2005	**Cases** 82 consecutive paediatric epilepsy patients **Diagnostic criteria** ILAE classifications **Controls** 49 **Inclusion criteria** • Cases were epilepsy patients visiting the Pediatric Epilepsy Center at	**Factors** Patients were classified according to the International League Against Epilepsy Classification. Risk factors • Seizure type • History of febrile convulsion Antibodies tested for: • Glutamate/AMPA receptor subtype 3 (Anti-GluR3B)	**Results** Proportion of epilepsy patients with positive test for GluR3B Ab's – all patients N=17/82 Proportion of positive antibody tests (GluR3B Ab's) in patients with partial epilepsy n=9/51 Proportion of positive antibody tests (GluR3B Ab's) in patients with generalised epilepsy n=8/20	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: High risk (period of recruitment was not described, exclusion criteria were not described, unsure if there was adequate participation of eligible individuals, very likely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if method of measurement is valid and reliable, unsure if method and setting of measurement of

Study details	Participants	Factors	Results	Comments
Ref Id 1066403 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort study **Study dates** Not mentioned **Consecutive recruitment** yes **Funding** Study was supported by grants to Levite M. from Volkswagen Stiftung and CURE (USA) citizens United for Research in Epilepsy Inc.	Schneider Children's Medical Center of Israel. • Control were patients admitted due to various non-neurological health problems (such as hypoglycemia, headaches, fever, proteinuria, kidney inflammation, liver enlargement, anemia, dysentery) to Schneider Children's Medical Center of Israel. • Controls were also sera samples drawn from healthy individuals who attended the blood bank to donate blood. **Exclusion criteria** Not mentioned **Statistical method** The non-parametric Kruskal–Wallis test was used and pairwise comparisons were performed by non-parametric Mann–Whitney U-test (the respective p-values reflect Bonferrani corrections) to compare the quantitative variables among the different groups of epilepsy patients. **Demographics** N=131	• Glutamate/NMDA receptor subunit 2A (Anti-NR2A) Evaluation of serum tests was based on an estimated threshold value, calculated separately for anti-GluR3B, anti-MR2A or anti-dsDNA Ab's as the mean antibody level of the control group + 2×S.D.	<u>Proportion of positive antibody tests (GluR3B Ab's) in patients with infantile spasms</u> n=0/11 <u>Proportion of positive antibody tests (Glutamate/NMDA) – all patients</u> n=15/82 <u>Proportion of positive antibody tests (Glutamate/NMDA) in patients with partial epilepsy</u> n=14/51 <u>Proportion of positive antibody tests (Glutamate/NMDA) in patients with generalised epilepsy</u> n=1/20 <u>Proportion of positive antibody tests (Glutamate/NMDA) in patients with infantile spasms</u> n=0/11 <u>Proportion of positive antibody tests (anti-dsDNA Ab's) – all patients</u> N=13/80 <u>Proportion of positive antibody tests (anti-dsDNA Ab's) in patients with partial epilepsy</u> n=6/49	prognostic factors is the same for all participants, unsure if adequate proportion of the study population has complete data for prognostic factors, may likely introduce substantial bias). **Outcome Measurement**: Moderate risk (unsure if outcome measurement was valid and reliable, blind measurement and confirmation with valid and reliable test was not mentions, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: High risk (unsure if statistical analysis is adequate, no regression model presented and unsure if all valid results were presented, very likely to introduce substantial bias). **Overall Quality: Low** **Other information** Note: Study did not report the number of individuals with a positive antibody test among the controls.

Study details	Participants	Factors	Results	Comments
	Cases: N=82 (N=51 patients with partial epilepsy; N=20 patients with generalised epilepsy; N=11 patients with infantile spasm). Control: N=49 (N=22 non-neurological health problems; N=27 healthy individuals). Cases only: Age (years), mean Partial epilepsy: 12.1 Generalised Epilepsy: 10.4 Infantile spasm: 6.3 Gender, number Partial epilepsy: Female: N=28 Male: N=23 Generalised Epilepsy: Female: N=8 Male: N=12 Infantile spasm: Female: N=5 Male: N=6		Proportion of positive antibody tests (anti-dsDNA Ab's) in patients with generalised epilepsy n=6/20 Proportion of positive antibody tests (anti-dsDNA Ab's) in patients with infantile spasms n=1/11	
Full citation Gozubatik-Celik, G., Ozkara, C., Ulusoy, C., Gunduz, A., Delil, S., Yeni, N., Tuzun, E., Anti-Neuronal Autoantibodies in Both	**Cases** 94 **Diagnostic criteria** ILAE classifications **Controls**	**Factors** Seizures and syndromes were diagnosed according to the International league Against Epilepsy (ILAE) commission on classification and terminology.	**Results** Proportion positive antibody tests (any) – all patients n=13/94	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias)

Study details	Participants	Factors	Results	Comments
Drug Responsive and Resistant Focal Seizures with Unknown Cause, Epilepsy research, 135, 131-136, 2017 **Ref Id** 1068021 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Study dates** 2009-2010 **Consecutive recruitment** Yes **Funding** Study was supported by the scientific research grants from Istanbul University and by an unconditional grant from Dem Pharma and Berk Pharma, Turkey.	50 **Inclusion criteria** • Cases were patients that gave their consent and were available for follow-up visits. • Patients with focal or diffuse atrophy or nonspecific white matter hyperintensities. • Patients with no current findings or past medical history of any neurological conditions. • Patients with systemic autoimmune disorders, febrile seizures or systemic infections with no direct temporal association between these medical conditions and the onset of seizures. • Patients with mesial temporal lobe epilepsy with hippocampal sclerosis. • Controls were age and gender matched healthy individuals. **Exclusion criteria** • Patients who were younger than 18 years	Risk factors: Seronegative and seropositive patients were compared in terms of: • Age at onset of seizures • Seizure type • History of febrile convulsion • Psychiatric or psychological disorder • Presence of immune related disorders • MRI abnormalities Antibodies tested for: • VGKC-complex LGI1 • CASPR-2 • NMDA-R • AMPA-R • GABAB-R • GAD	Proportion of epilepsy patients with positive AMPA-R test n=1/94 Proportion of epilepsy patients with positive anti-CASPR-2 test n=0/94 Proportion of epilepsy patients with positive anti-GABAB-R test n=0/94 Proportion of epilepsy patients with positive anti-LGI1 test n=0/94 Proportion of epilepsy patients with positive GAD test n=4/94 Proportion of epilepsy patients with positive NMDA-R test n=1/94 Proportion of epilepsy patients with positive anti-VGCC test n=0/94 Proportion of epilepsy patients with positive VGKC-complex test n=5/94 Proportion of positive antibody tests (any antibody) in patients with a history of febrile convulsions n=1/12	**Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (unsure if method of measurement of prognostic factors is valid and reliable, but unlikely to introduce substantial bias). **Outcome Measurement**: Moderate risk (unsure if outcome measurement was valid and reliable, blind measurement and confirmation with valid and reliable test was not mentions, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure if statistical model is adequate, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low** Two patients had an elevated titre to multiple antigens (VGKC-complex and GAD). Although some information is reported in regards to psychiatric status, insufficient detail is provided to report data on this.

Study details	Participants	Factors	Results	Comments
	at the time of blood sampling or had structural lesions in brain magnetic resonance imaging (MRI) such as tumor or dysplasia. **Statistical method** Comparisons were made by independent sample t-test or Fisher's exact test when data were distributed homogenously and by Mann-Whitney U test when distributed heterogeneously for quantitative data and by X^2 test for qualitative data. The p level< 0.05 was accepted as significant. SPSS 15 was used. **Demographics** N=144 Cases: N=94 Epileptic patients with focal seizure of unknown cause. Control: N=50 age-and-gender matched healthy individuals Age (years), range; mean ± SD Cases: 18-84 years; 37.5±15 years Control: 21-77 years; 30.1±11.8 years Age at seizure onset (years), range; mean ± SD		Proportion of positive antibody tests (any antibody) in patients with a history of inflammatory/autoimmune events (e.g. systemic lupus erythematosus, diabetes mellitus type I, Hashimoto's thyroiditis, pernicious anaemia and psoriasis) n=9/33 Proportion of positive antibody tests (any antibody) in patients with MRI abnormalities – white matter lesions n=2/8 Proportion of positive antibody tests (any) in patients with MRI abnormalities (hippocampal sclerosis) n=0/8	

Study details	Participants	Factors	Results	Comments
	Cases only: 4-84 years; 27±16.3 years Gender, number Cases: Female: N=39 Male: N=55 Control: Female: N=22 Male: N=22			
Full citation Liimatainen, S., Peltola, M., Sabater, L., Fallah, M., Kharazmi, E., Haapala, A. M., Dastidar, P., Knip, M., Saiz, A., Peltola, J., Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy, Epilepsia, 51, 760-7, 2010 **Ref Id** 1068608 **Country/ies where the study was carried out** Finland **Study type** Prospective cohort study	**Cases** 253 patients with epilepsy **Diagnostic criteria** ILAE classification **Controls** 200 **Inclusion criteria** • Cases were adult patients with epilepsy and recurrent seizures treated in the Outpatient Clinic of Neurology and Rehabilitation, Tampere University Hospital between January 2003 and November 2005. • Controls were non-diabetic organ donors without any history of epilepsy. (The complete knowledge of associated autoimmune diseases	**Factors** Focal epilepsy types were categorized according to the International League Against Epilepsy (ILAE) guidelines. Risk factor • Presence of other autoimmune disease Antibodies tested for: • GADA (high titers: ≥1,000 RU/ml and associated autoimmune disease; low titers <1,000 RU/ml without associated autoimmune diseases). • TPO (TPO antibodies was tested only in GADA positive patients and a randomly selected 47-56 GADA negative patients with focal epilepsy).	**Results** Proportion of positive antibody tests - (GADA) – all patients N=15/253 (n=7 high GADA titre; n=8 low GADA titre) Proportion of epilepsy patients with a positive test for GADA who also tested positive for TPO GADA positive case n=5/15	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was adequate participation of eligible individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (unsure if method of measurement of prognostic factors is valid and reliable, unsure if method and setting of measurement is the same for all participants, but unlikely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (Unsure of the confounders adjusted for, no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure of the adequacy of the stated regression model, un-

Study details	Participants	Factors	Results	Comments
Study dates January 2003 - November 2005 **Consecutive recruitment** Yes **Funding** Medical Research Fund of Tampere University Hospital.	was lacking in the control group). **Exclusion criteria** • Patients with dementia or high-grade brain tumor and epilepsy. • Mentally handicapped patients. **Statistical method** For the univariate analysis of the categorical variables, Fisher's exact test was performed when X^2 test was not applicable (such as the association between having high levels of GADA and having focal/generalized epilepsy). Univariate/ multivariate logistic regression analysis was applied when crude/fully adjusted odds ratio (OR) was needed. All analyses were performed using Stata 8th version. **Demographics** N=453 Cases: N= 253 (patients with focal epilepsy and idiopathic generalised epilepsy) (n=34 idiopathic generalised epilepsy (IGE); n=139 temporal			sure if all relevant results were presented, may likely introduce substantial bias). **Overall Quality: Low** **Other information** Note: • Number of patients with epilepsy (Extra TLE, TLE and IGE) added up to 243 and not 253. • It was reported that in 10 patients, focal epilepsy type was unknown; hence the epilepsy type was considered as Extra TLE. However, study included patients with focal, multifocal or unknown focal epilepsy patients.

Study details	Participants	Factors	Results	Comments
	lobe epilepsy (TLE); n=70 Extra-TLE) Control: N=200 (non-diabetic organ donors) Age (years), range; mean Cases: 16-76 years; 38.9 years Control: 15-72 years; 44.9 years Gender, (%) Cases: Female: 53.4; male: 46.6 Control: Female: 38.5; male: 61.5			
Full citation Majoie, H. J. M., de Baets, M., Renier, W., Lang, B., Vincent, A., Antibodies to voltage-gated potassium and calcium channels in epilepsy, Epilepsy Research, 71, 135-141, 2006 **Ref Id** 1068618 **Country/ies where the study was carried out** Netherlands	**Cases** 106 **Diagnostic criteria** ILAE classification **Controls** 150 **Inclusion criteria** • Cases were female epilepsy patients who visited the outpatient clinic of a tertiary referral clinic (Epilepsy Centre Kempenhaeghe). • Controls were previously reported individuals with	**Factors** Epilepsy and seizure were classified according to the International League Against Epilepsy classification. Risk factors • Age • Cognition (level of cognitive function was entered into the database using a 3-point scale (normal IQ, borderline IQ, subnormal IQ). • Presence of other auto immune diseases • Seizure type	**Results** Proportion of positive antibody tests – all patients N=7/106 (GAD n=1; VGKC n=6; VGCC n=1)	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Moderate risk (period of recruitment was not described, exclusion criteria were not described, unsure if there was adequate participation of eligible individuals, may likely introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (unsure if method of measurement of prognostic factors was valid and reliable, unsure if method and setting of measurement was the same for all participants, but unlikely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain)

Study details	Participants	Factors	Results	Comments
Study type Retrospective case control study **Study dates** Not mentioned **Consecutive recruitment** Yes **Funding** Not mentioned	multiple sclerosis, stroke, other neurologic diseases and healthy individuals only. **Exclusion criteria** Not mentioned. **Statistical method** Summary statistics present mean, standard deviation, median, minimum, and maximum values for continuous variables and frequencies and percentages for categorical variables. The correlation between the different variables and the presence of antibodies was tested with the Pearson X^2 tests. **Demographics** N=256 Cases: N=106 (female patients with epilepsy) Control: N= 150 (n=50 with multiple sclerosis, n=62 with stroke, n=19 with other neurological diseases and n=19 healthy individuals). <u>Age (years), mean</u> seropositive cases: 34.9 years seropositive cases: 31.4 years	<u>Antibodies tested for:</u> • VGKC and VGCC-antibodies (P/Q and N type)-(positive titre level>100pM) • GAD		**Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure of the adequacy of the statistical model, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low** **Other information**

Study details	Participants	Factors	Results	Comments
	Range for cases only: 15-45 years Gender, number Cases only: female: N=106			
Full citation Niehusmann, P., Dalmau, J., Rudlowski, C., Vincent, A., Elger, C. E., Rossi, J. E., Bien, C. G., Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy, Archives of Neurology, 66, 458-464, 2009 **Ref Id** 1066673 **Country/ies where the study was carried out** Germany **Study type** Prospective cohort study **Study dates**	**Cases** 19 **Diagnostic criteria** Not mentioned **Controls** 72 **Inclusion criteria** • Cases were female patients ages 14-45 years with unexplained new onset epilepsy (such as those who had recurrent seizures starting in the past 5 years with neither an obvious provoking factor nor an apparent remote origin, such as a brain malformation or tumor, trauma, central nervous system infection, or idiopathic generalized epilepsy). • Control were patients older than 15 years with unexplained new-onset	**Factors** Risk factors • MRI abnormalities • Psychiatric or psychological disorder • Presence of encephalopathy • MRI abnormalities Antibodies tested for: • VGKC antibodies (low positive titre level: 100-400 pmol/L; high positive titres: >400 pmol/L) • GAD antibodies (positive titre level >0.6U/mL) • NMDAR antibodies (NR1/NR2 heteromers) • TPO antibodies (reference range <40U/mL) Note: GAD and NMDAR antibodies were not tested for in all the control patients. TPO antibodies were not reported tested for in the control patients.	**Results** Proportion of positive antibody test (any) – all patients n=5/19	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Moderate risk (epileptic diagnostic criteria was not reported, may likely introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: High risk (no definition was provided for prognostic factors, unsure if method of measurement of prognostic factors was valid and reliable, unsure if method and setting of measurement was the same for all participants, unsure if adequate proportion of study population had complete data, very likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure statistical model was adequate, no regression model presented, unsure if all relevant results were presented, very likely to introduce substantial bias). **Overall Quality: Low**

Study details	Participants	Factors	Results	Comments
January 1 2005-June 30 2007 **Consecutive recruitment** Yes **Funding** Study was supported in part by grants to Dalmau J. from the National Cancer Institute, National Institutes of Health.	epilepsy (“cryptogenic epilepsies”) presenting in the same period underwent CSF and serum studies for routine investigation. [Control group 1]. • Control were patients with epilepsy treated surgically for pharmacoresistant epilepsy with non-inflammatory histopathologic findings (hippocampal sclerosis; tumor; dysplasia; and nonspecific). [Control group 2]. **Exclusion criteria** • Female inpatients during the study period with chronic epilepsy with a history longer than 5 years, with a distinct lesional epilepsy cause, or were outside the indicated age range. **Statistical method** For nominal data, Fisher 2-sided exact tests, and for metric data, 2-sided Mann-Whitney tests, were applied. SPSS 14.0 was used. **Demographics** N=91			**Other information** Seizures were reported but could not be separated to calculate proportions.

Study details	Participants	Factors	Results	Comments
	Cases: N=19 (female in-patients with unexplained new onset epilepsy). Control: N=72 (n=61 with cryptogenic epilep-sies [control groups 1]; n=11 with surgically treated epilepsy [control group 2]). Age (years), range; means ± SD Cases: 16-44 years; 26±9 years. Control group 1: 55±16 years (range not re-ported). Control group 2: 46±9 years (range not re-ported). Gender, number Cases: Female: N=19 Control group 1: Female: N=24 Male: N=37 Control group 2: Female: N=4 Male: N=7			
Full citation Tecellioglu, M., Ka-misli, O., Kamisli, S., Yucel, F. E., Ozcan,	**Cases** N=77 **Diagnostic criteria** ILAE classification	**Factors** Seizure and syndromes were diagnosed according to the international League Against Epilepsy (ILAE)	**Results** Proportion of positive antibody tests – all patients N=17/77 (ANA n=8; TPO n=4; GAD n=1; VGKCc n=4; onconeu-ral antibodies n=2)	**Limitations** QUIPS Checklist: Risk of Bias Assess-ment **Study Participation**: Low risk (no area of concern for this domain)

Study details	Participants	Factors	Results	Comments
C., Neurological autoantibodies in drug-resistant epilepsy of unknown cause, Irish Journal of Medical Science, 187, 1057-1063, 2018 **Ref Id** 1068361 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Study dates** July 2016-July 2017 **Consecutive recruitment** Yes **Funding** İnönü University Scientific Project Unit.	**Inclusion criteria** • Patients with drug resistant epilepsy of unknown cause were prospectively included in this study. • Patients were over 18 years old. • Patients without any neurological signs or neurological diseases other than epilepsy. **Exclusion criteria** • Structural brain lesions (ischaemia, tumour, head trauma, vascular malformation, abscess, congenital malformation, heterotypic conditions). • Metabolic abnormalities (severe hypoglycaemia or hyperglycaemia, severe renal or hepatic deficiency, malignant hypertension, alcoholism). • Proven or suspected chromosomal anomalies and genetic syndromes. • Any malignancy. **Statistical method** Statistical analyses were performed using SPSS	Commission on Classification and Terminology 2017. <u>Risk factors</u> • Age at seizure onset • MRI abnormalities • Seizure type • Neuropsychiatric changes <u>Antibodies tested for:</u> • VGKC complex antibodies • TPO antibodies • GAD antibodies • onconeural antibodies		**Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (unsure if method of measurement of prognostic factors was valid and reliable, but unlikely to introduce substantial bias). **Outcome Measurement**: Moderate risk (unsure if method of outcome measurement is adequately valid and reliable, no blind measurement and confirmation of outcome with valid and reliable test, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure statistical model was adequate, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low**

Study details	Participants	Factors	Results	Comments
	15. Comparisons were performed using independent samples t tests and Fisher's exact tests when the data were distributed homogenously; the Mann–Whitney U test was used for quantitative data, and the X^2 test was used for heterogeneously distributed qualitative data. In all analyses, $p < 0.05$ indicated statistical significance. **Demographics** N=77 with drug resistant epilepsy of unknown cause Antibody positive: N=17 Antibody negative: N=60 Age (years), mean±SD 33.6±11.3 years Gender, number Female: N=29 Male: N=48 Antibody positive: Female: N=10 Male: N=7 Antibody negative: Female: N=19 male: N=41			
Full citation	**Cases**	**Factors**	**Results**	**Limitations**

Study details	Participants	Factors	Results	Comments
Tekturk, P., Baykan, B., Erdag, E., Peach, S., Sezgin, M., Yapici, Z., Kucukali, C. I., Vincent, A., Tuzun, E., Investigation of neuronal auto-antibodies in children diagnosed with epileptic encephalopathy of unknown cause, Brain and Development, 40, 909-917, 2018 **Ref Id** 1068363 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Study dates** 2012-2014 **Consecutive recruitment** Yes **Funding**	50 consecutive patients with epileptic encephalopathies **Diagnostic criteria** ILAE classification **Controls** 40 **Inclusion criteria** • Cases were patients who were followed in Istanbul Faculty of Medicine, Department of Child Neurology unit between 2012 and 2014 and had been diagnosed as epileptic encephalitis. • Controls were age and gender-matched healthy volunteers. **Exclusion criteria** • Patients with tuberous sclerosis **Statistical method** Descriptive statistics were applied, and the 2 groups of patients with and without serum antibodies were compared with Fisher's exact test, X^2 test and independent samples t-test,	Seizures and syndromes were diagnosed according to the International League Against Epilepsy Commission on Classification and Terminology. Risk factors • Age • Seizure type • Status epilepticus • Presence of febrile seizure • History of autoimmune disorders • Cognitive impairment (Denver or Alexander tests were used depending on the age of the subjects) • Neurological abnormalities (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. • MRI abnormalities Antibodies tested for: • VGKC-complex	Proportion of positive antibody tests (any) in all patients N=7/50 (NMDA-R n=2; $GABA_AR$ n=1; CASPR2 n=1; GAD n=1; glycine receptor n=2) LGI1, VGKC-complex and AMPAR antibodies were not found in any patient with epilepsy Proportion of positive antibody tests (any) in patients with multifocal focus epilepsy n=4/32 Proportion of positive antibody tests (any) in patients with MRI abnormalities n=4/20 Proportion of positive antibody tests (any) in patients with a history of status epilepticus n=0/9 Proportion of positive antibody tests (any) in patients with a history of febrile seizures n=1/3	QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was an adequate participation of eligible individuals but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Low risk (no area of concern for this domain). **Outcome Measurement**: Moderate risk (unsure if outcome measurement was valid an reliable, blind measurement and confirmation with valid and reliable test was not mentions, may likely introduce substantial bias) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure statistical model was adequate, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low**

Study details	Participants	Factors	Results	Comments
Study was supported by the Turkish Scientific and Technical Research Council.	where appropriate. SPSS 15 was used and the significance level was set at $p < 0.05$. **Demographics** N=90 Cases: N=50 (patients with epileptic encephalopathy of unknown cause) Control: N=40 (age-and gender matched healthy volunteers). Age (years), range; mean ± SD Cases only: 1-36 years; 10.84±8.89 years Age at onset of seizure (years), range; mean ± SD Cases only: 1-14 years; 22.54±34.23 years Gender, number Female: N=18 Male: N=32 Seropositive patients: Female: N=2 Male: N=5 Seronegative patients: Female: N=16 Male: N=27 72% of the study group had received immunotherapy (ACTH in all patients) before serum sampling.	• LGI1 • CASPR2 NMDAR • GLYR • GAD • AMPAR $GABA_AR$		
Full citation	**Cases**	**Factors**	**Results**	**Limitations**

Study details	Participants	Factors	Results	Comments
Veri, K., Uibo, O., Talvik, T., Talvik, I., Metskula, K., Napa, A., Vaher, U., Oiglane-Slik, E., Rein, R., Kolk, A., Traat, A., Uibo, R., Newly-diagnosed pediatric epilepsy is associated with elevated autoantibodies to glutamic acid decarboxylase but not cardiolipin, Epilepsy research, 105, 86-91, 2013 **Ref Id** 1067298 **Country/ies where the study was carried out** Estonia **Study type** Prospective cohort study **Study dates** January 2009 to April 2011 **Consecutive recruitment**	208 **Diagnostic criteria** ILAE classifications **Controls** 128 **Inclusion criteria** • Cases were paediatric patients who were admitted to the Children's Clinic of Tartu University Hospital between January of 2009 and April of 2011. • Control were included patients with functional urinary (enuresis) and gastrointestinal (abdominal pain, constipation) disorders admitted to the Children's Clinic of Tartu University Hospital. • Patients with acute illness, coexisting autoimmune and neurological disorders. **Exclusion criteria** • Neonatal seizures and cases with only febrile seizures.	Epilepsy was confirmed according to the recommendations of the International League Against Epilepsy. Antibody tested for: • GAD65 antibody (positive threshold ≥5 U/ml) • ACA (positive threshold ≥12 RU/ml)	Proportion of positive antibody test (any) – all patients N=15/208 (GADA n=14; ACA n=13) (focal idiopathic epilepsy n=5; focal symptomatic epilepsy n=2; generalised idiopathic epilepsy n=2; generalised symptomatic epilepsy n=1; unclassified epilepsy n=4). Most patients with epilepsy (n= 11) displayed a low GADA level (5—38 U/ml), but three had GADA values >50 U/ml,	QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (unsure if there was an adequate participation of eligible individuals but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: High risk (no definition was provided for prognostic factors, unsure if method measurement of prognostic factor was valid and reliable, unsure if method and setting of measurement was the same for all participants, unsure if adequate proportion of the study participants had complete data, very likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: High risk (unsure statistical model was adequate, no regression model presented, unsure if all relevant results were presented may likely introduce substantial bias). **Overall Quality: Low** **Other information** Note: • There was no difference in terms of demographic characteristics between GADA positive and negative patients

Study details	Participants	Factors	Results	Comments
Yes **Funding** Study was supported by the Estonian Science Foundation, Grant; by targeted financial support from the Estonian Ministry of Education and Research; and by the European Union through the European Regional Development Fund.	**Statistical method** • Statistical analysis was performed using X^2 test and Fisher's exact test. **Demographics** N=336 Cases: N=208 (children with newly diagnosed epilepsy) Control: N=128 (children with urinary and gastrointestinal disorders) Age(years), range; mean Cases: 1 month -19 years; 7.8 years Control: 2-18 years; 9.5 years **Gender, number** Cases: Female: N=99 Male: N=109 Control: Female: N=64 Male: N=64			
Full citation Verrotti, A., Greco, R., Altobelli, E., Latini, G., Morgese, G., Chiarelli, F., Anticardiolipin, glutamic acid decarboxylase, and antinuclear antibodies	**Cases** 74 **Diagnostic criteria** ICEES Classification **Controls**	**Factors** Type of epilepsy was determined according to the International Classification of Epilepsies and Epileptic Syndromes classification. Antibody tested for:	**Results** Proportion of positive antibody tests (acL) – all patients N=20/74 Proportion of positive antibody tests (ANA) – all patients N=22/74	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Moderate risk (sampling frame was not adequately described, period of recruitment was not mentioned, unsure if there was an adequate participation of eligible individuals may likely introduce substantial bias)

Study details	Participants	Factors	Results	Comments
in epileptic patients, Clinical & Experimental Medicine, 3, 32-6, 2003 **Ref Id** 1068693 **Country/ies where the study was carried out** Italy **Study type** Prospective case control study **Study dates** Not mentioned **Consecutive recruitment** Not mentioned **Funding** Not mentioned.	50 **Inclusion criteria** • Cases were children suffering from different types of epilepsy who were treated with various anticonvulsants (ASMs) and were seizure free for at least 1 year. (Group I). • Cases were children suffering from therapy resistant epilepsy. (Group 2). • Control were sex and age-matched children who did not suffer from any neurological or endocrine diseases. **Exclusion criteria** • Laboratory or clinical signs of autoimmune disease, lymphoproliferative disorders, chronic or acute infectious disease, and therapy with drugs that can induce systemic lupus erythematosus. **Statistical method** • Anticardiolipin (aCL), GAD and antinuclear antibody (ANA) antibody	• acL • ANA • GAD	Proportion of positive antibody tests (GAD) – all patients N=4/74	**Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: High risk (no definition was provided for prognostic factors, unsure if method measurement of prognostic factor was valid and reliable, unsure if method and setting of measurement was the same for all participants, unsure if adequate proportion of the study participants had complete data, very likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure statistical model was adequate, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low** **Other information** Note: • There was no reported significant difference between the characteristics of children in the three group.

Study details	Participants	Factors	Results	Comments
	positivity was compared between groups by a X^2 test and Fischer's exact test when appropriate. Statistical analysis was performed using SPSS 6.0. Correlations were calculated using Spearman's rank correlation coefficient. P<0.05 was considered statistically significant. **Demographics** N=124 Case Group 1: N=52 (children with seizure free epilepsy) Case Group 2: N=22 (children with drug resistant epilepsy) Control: N=50 (age-and gender matched healthy children) Age(years), mean±SD Case Group 1: 7.0±2.4 years Case Group 2: 6.2±3.6 years Gender, number Case Group 1: Female: N=30 Male: N=22 Case Group 2: Female: N=10 Male: N=12			

Study details	Participants	Factors	Results	Comments
Full citation Wright, S., Geerts, A. T., Jol-Van Der Zijde, C. M., Jacobson, L., Lang, B., Waters, P., Van Tol, M. J. D., Stroink, H., Neuteboom, R. F., Brouwer, O. F., Vincent, A., Neuronal antibodies in pediatric epilepsy: Clinical features and long-term outcomes of a historical cohort not treated with immunotherapy, Epilepsia, 57, 823-831, 2016 **Ref Id** 1068703 **Country/ies where the study was carried out** Netherlands **Study type** Multi-centre retrospective cohort study **Study dates** 1988-1992 **Consecutive recruitment** Yes **Funding** Oxford University/Wellcome	**Cases** 178 paediatric epilepsy patients *without* encephalitis. **Diagnostic criteria** ILAE Classification **Controls** 112 **Inclusion criteria** • Cases were children (aged 1 month to 16 years) who were enrolled into the Dutch Study of Epilepsy in Childhood (DSEC) from four participating centers in The Netherlands between 1988 and 1992. • Controls were age and sex-matched control samples from age-matched sibling donors of bone marrow transplantations (BMTs), collected between 1985 and 1995 and stored under the same condition as the patients' sera. **Exclusion criteria**	**Factors** Risk factors Antibody positive and antibody negative case patients were compared on • Neurological abnormalities • Mental retardation/cognitive impairment at intake • History of febrile seizures before or after intake • status epilepticus. • Seizure type at onset reported only for antibody positive patients Antibodies tested for: • VGKC complex (positive titre level was >400 pM) • GAD (positive titre level was at >100 units/ml) • NMDAR • AMPAR • LGI1 • CASPR2 • Contactin-2 Note: Follow-up serum samples from 96 patients taken at 6 months (N = 30), 12 months (n = 34), and 6	**Results** Proportion of positive antibody tests (any) – all patients N=17/178 (VGKC complex [n=3]; NMDAR [n=7], CASPR2 [n=4]; contactin-2 [n=3]) Antibodies to LGI1, AMPAR, or GAD were not identified in any patients or controls Proportion of positive antibody tests (any) in patients with cognitive impairment/developmental delay at intake n=9/42 Proportion of positive antibody tests (any) in patients with a history of febrile seizures before or after intake n=1/33 Proportion of positive antibody tests (any) in patients with pre-existing neurologic signs/abnormal examination n=3/20 Proportion of positive antibody tests (any) in patients with status epilepticus as a presenting feature n=2/11	**Limitations** QUIPS Checklist: Risk of Bias Assessment **Study Participation**: Low risk (no area of concern for this domain) **Study Attrition**: Low risk (there was a drop in response rate at follow up, but unlikely to introduce substantial bias) **Prognostic Factor Measurement**: High risk (no definition was provided for prognostic factors, unsure if method measurement of prognostic factor was valid and reliable, unsure if method and setting of measurement was the same for all participants, unsure if adequate proportion of the study participants had complete data, very likely to introduce substantial bias). **Outcome Measurement**: Low risk (no area of concern for this domain) **Study Confounding**: High risk (no definition or measurement reported for confounders) **Statistical Analysis and Reporting**: Moderate risk (unsure statistical model was adequate, no regression model presented, may likely introduce substantial bias). **Overall Quality: Low** **Other information** Note: • Study reported result for contactin-2 antibodies.

Study details	Participants	Factors	Results	Comments
Trust Clinical Research Training Fellowship; and NIHR Oxford Biomedical Research Centre.	• Children with a presumed 'acute symptomatic' aetiology for their epilepsy (defined as seizures occurring only during the first week after the onset of acute neurologic insult, for example, stroke, head trauma, or central nervous system infection, or concurrently with an acute systemic metabolic disturbance, for example, uremia, hyponatremia, or hypoglycemia, or both). **Statistical method** Descriptive statistics were used to summarize patient data. Fisher's exact test was used to compare categorical data. Data analysed using GraphPad Prism 6.0. **Demographics** N=290 Cases: N=178 (Children with epilepsy with and without encephalitis) Control: N=112 (age-and gender matched sibling donors of bone marrow transplantation). <u>Age (years), range</u>	and 12 months (N = 32) after intake were reported available for testing.		

Study details	Participants	Factors	Results	Comments
	Cases: 1 month-16 years Antibody positive cases only: 0.9-15.5 years Antibody negative case only: 0.2-15.8 years Gender, number Antibody positive cases only: Female: N=8 Male: N=9 Antibody negative case only: Female: N=89 Male: N=72			

Ab's: Antibodies, ACA: Anticentromere antibody; aCL: Anticardiolipin; ASM: antiseizure medication; AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPA-R: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANA: Antinuclear antibody; BMT: Bone marrow transplantation; CASPR-2: Contactin-associated protein 2; CRMP5: Collapsin response mediator protein 5; CSF: Cerebrospinal fluid; CURE: Citizens United for Research in Epilepsy Inc.; DNA: Deoxyriboneucleic acid; dsDNA: Double strand deoxyriboneucleic acid; DSEC: Dutch Study of Epilepsy in Childhood; EEG: Electroencephalogram; GABA(A)R: Gamma aminobutyric acid (type A) receptor; GABA(B)R: Gamma aminobutyric acid (type B) receptor; GAD: Glutamic acid decarboxylase; GADA/ GAD-ab: Glutamic acid decarboxylase antibodies; GluR3: Glutamate receptor 3; GluR3B: Autoantibodies to the "B" peptide (amino acids 372-395) of glutamate receptor 3; GLY-R: Glycine receptor; GM1: Monosialotetrahexosylganglioside; HEK293: Human Embryonic Kidney cells; HS: Hippocampal sclerosis; ICEES: International Classification of Epilepsies and Epileptic Syndromes; IGE: Idiopathic generalised epilepsy; ILAE: International League Against Epilepsy; IQ: Intelligence quotient; JME: Juvenile myoclonic epilepsy; LGI1: Leucine-rich glioma inactivated-1; MR2A: Mental Retardation, Autosomal Recessive 2A; MRI: Magnetic resonance imaging; MTLEHS: Mesial temporal lope epilepsy with hippocampal sclerosis; NIHR: National Institute for Health Research; NMDA: N-methyl-d-aspartate; NMDA-R: N-methyl-d-aspartate receptor; OR: Odds ratio; pmol/L: Picomoles per litre; QUIPS: Quality In Prognosis Studies; RRMS: Relapsing-remitting multiple sclerosis; RU/ml: Relative units per millilitre; SD: Standard deviation; SE: Status epilepticus; SPSS: Statistical Package for the Social Sciences; TLE: Temporal lobe epilepsy; TPO: Thyroid peroxidase; U/ml: Units per millilitre; VGCC: Voltage gated calcium channel; VGKC: Voltage gated potassium channel; VGKCc: Voltage gated potassium channel complex

Appendix E – Forest plots

Forest plots for review question: In people with epilepsy, who should have antibody testing?

No meta-analysis was conducted for this review question due to variation in the evidence regarding antibodies tested for. As a result, there are no forest plots.

1 Appendix F – Adapted GRADE tables

2 **Table 5: Clinical evidence profile for proportion with positive antibody test in all studies**

Quality assessment							Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of % case positive, n (%)	Quality	Importance
Proportion of positive antibody test in patients with epilepsy										
1 (Ganor 2005)	Observational study	• Gluta-mate/NMDA	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	82	15/82 (18)	⊕OOO VERY LOW	CRITICAL
1 (Ganor 2005)	Observational study	• Anti-dsDNA Ab's	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	80	13/80 (16)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test in patients with status epilepticus of unidentified origin										
1 (Atmaca 2017)	Observational studies	• NMDA-R • GLY-R • $GABA_AR$	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	22	5/22 (22.7)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Focal epilepsy and no sign of encephalitis										
1 (Borusiak 2016)	Observational studies	• GAD65 • VGKC	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	124	5/124 (4)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Treatment resistant MTLEHS and mostly easy to treat JME										
1 (Ceyhan Dirican 2016)	Observational studies	• GADA	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	54	3/54 (6)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Focal and generalized epilepsy										

Quality assessment							Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of % case positive, n (%)	Quality	Importance
1 (Errichiello 2009)	Observational studies	• GAD65	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	233	6/233 (3)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – TLE of unknown aetiology known and unknown aetiology										
1 (Falip 2012)	Observational studies	• GADA	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	42	5/42 (12)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Partial epilepsy; generalised epilepsy and infantile spasm.										
1 (Ganor 2005)	Observational studies	• Glutamate/AMPA receptor subtype 3 • Glutamate/NMDA receptor subunit 2A	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	82	Glutamate/AMPA: 17/82 (21) Glutamate/NMDA: 15/82 (18)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (any) test in patients with focal seizures of unknown cause										
1	Observational studies	• AMPA-R	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	94	13/94 (14)	⊕OOO VERY LOW	CRITICAL

Quality assessment							Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of % case positive, n (%)	Quality	Importance
(Gozubatik-Celik 2017)		• Anti-CASPR-2 • Anti-GABAB-R • Anti-LGI1 • GAD • NMDA-R • VGKC-complex								
Proportion of positive antibody test – Focal epilepsy and idiopathic generalised epilepsy										
1 (Liimatainen 2010)	Observational studies	• GADA • GADA and TPO¥	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	253	15/253 (6)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Female patients with epilepsy										
1 (Majoie 2006)	Observational studies	• VGKC • GADA and VGKC	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	106	7/106 (7)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Unexplained new onset epilepsy										
1 (Niehusmann 2009)	Observational studies	• NMDAR	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	19[3]	NMDAR: 5/19 (26)	⊕OOO VERY LOW	CRITICAL

Quality assessment							Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of % case positive, n (%)	Quality	Importance
Proportion of positive antibody test – Drug resistant epilepsy of unknown cause										
1 (Tecel-lioglu 2018)	Observational studies	• VGKC and anti-nuclear antibod-ies • VGKC and TPO • TPO • VGKC • GAD • Intracellu-lar anti-gens (Yo and MA2/TA)	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	77	17/77 (22)[4]	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Epileptic encephalopathy of unknown cause										
1 (Tekturk 2018)	Observational studies	• NMDAR • GABAAR • CASPR2 • GAD • GLYR	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	50	7/50 (14)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Newly diagnosed epilepsy										

Quality assessment							Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of % case positive, n (%)	Quality	Importance
1 (Veri 2013)	Observational studies	• GAD65	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	208	15/208 (7)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Controlled and uncontrolled epilepsy										
1 (Verrotti 2003)	Observational studies	• acL	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	74	20/74 (27)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Controlled and uncontrolled epilepsy										
1 (Verrotti 2003)	Observational studies	• ANA	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	74	22/74 (30)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Controlled and uncontrolled epilepsy										
1 (Verrotti 2003)	Observational studies	• GAD	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	74	4/74 (5)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody test – Epilepsy with and without encephalitis										
1 (Wright 2016)	Observational studies	• VGKC complex • NMDAR • CASPR2 • Contac-tin-2	Serious[1]	No serious in-consistency	No serious indirectness	Very serious[2]	178	17/178 (10)¶	⊕OOO VERY LOW	CRITICAL

1 *¥TPO antibody was tested only in GADA positive patients and a randomly selected 47-56 GADA negative patient with focal epilepsy*
2 *δGAD and NMDAR antibodies were not tested for in all the control patients*
3 *ŸVGKC TPO antibodies were not reported as tested for in the control patients*

¶*Study reported N=3 patients tested positive for antibodies to contactin-2*
1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150
3 Control were 72 with cryptogenic (61) and surgery treated epilepsy (11)
4 N=8 patients were positive for antinuclear antibodies

Table 6: Clinical evidence profile for proportion of positive antibody test in patients with cognitive impairment

	Quality assessment						Number of patients			
Number of studies	Design	Antibodies found	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody tests in patients with cognitive impairment/developmental delay at intake										
1 (Wright 2016)	Observational studies	Multiple antibodies[a]	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	42	9/42 (21)	⊕OOO VERY LOW	CRITICAL

a VGKC, GAD, NMDAR, AMPAR, LGI1, CASPR2, Contactin-2
1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

Table 7: Clinical evidence profile for proportion of positive antibody test in patients with a history of febrile seizures

Quality assessment						Number of patients			
Quality	Importance	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody in patients with a history of febrile seizures – patients with status epilepticus of unidentified origin									
1 (Atmaca 2017)	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	5	1/5 (20)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody according to history of febrile seizures – patients with confirmed epilepsy									
1 (Gozubatik-Celik 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	12	1/12 (8)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody according to history of febrile seizures – patients with epileptic encephalitis									
1 (Tekturk 2018)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	3	1/3 (33)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody according to history of febrile seizures – children with epilepsy									
1 (Wright 2016)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	33	1/33 (3)	⊕OOO VERY LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

Table 8: Clinical evidence profile for proportion of positive antibody test according to neurological abnormalities

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody in patients with pre-existing neurologic signs/abnormal examinations									
1 (Wright 2016)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	20	3/20 (15)	⊕OOO VERY LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

Table 9: Clinical evidence profile for proportion of positive antibody test in patients with inflammatory/autoimmune events

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody tests in patients with inflammatory/autoimmune events									
1 (Gozubatik-Celik 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	33	9/33 (23)	⊕OOO VERY LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

Table 10: Clinical evidence profile for proportion of positive antibody test in patients with psychiatric or psychological disorders

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody in those with psychiatric or psychological disorder									
1 (Atmaca 2017)	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	4	1/4 (25)	⊕OOO VERY LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

Table 11: Clinical evidence profile for proportion of positive antibody test in patients with MRI abnormalities

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody tests in patients with MRI abnormalities									
1 (Atmaca 2017)	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	11	3/11 (27)	⊕OOO VERY LOW	CRITICAL

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
1 (Tekturk 2018)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	20	4/20 (20)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests in patients with MRI abnormalities – white matter lesions									
1 (Gozubatik-Celik 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	8	2/8 (25)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests in patients with MRI abnormalities – hippocampal sclerosis									
1 (Gozubatik-Celik 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	8	0/8 (0)	⊕OOO VERY LOW	CRITICAL

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist*
2 *2 Number of events <150*

3

1 **Table 12: Clinical evidence profile for proportion of positive antibody test according to epilepsy/seizure type**

Quality assessment						Number of patients		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)		
Proportion of positive antibody (GluR3B Ab's) according to seizure type – partial epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	51	9/51 (18)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (GluR3B Ab's) according to seizure type – generalised epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	20	8/20 (40)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (GluR3B Ab's) according to seizure type – infantile spasms									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	11	0/11 (0)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (Glutamate/NMDA) according to seizure type – partial epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	51	14/51 (27)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (Glutamate/NMDA) according to seizure type – generalised epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	20	1/20 (5)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (Glutamate/NMDAR) according to seizure type – infantile spasms									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	11	0/11 (0)	⊕OOO VERY LOW	CRITICAL

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody (anti-dsDNA Ab's) according to seizure type – partial epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	49	6/49 (12)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (anti-dsDNA Ab's) according to seizure type – generalised epilepsy									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	20	6/20 (30)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (anti-dsDNA Ab's) according to seizure type – infantile spasms									
1 (Ganor 2005)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	11	1/11 (10)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody (anti-dsDNA Ab's) according to seizure type – multifocal focus epilepsy									
1 (Tekturk 2018)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	32	4/32 (12)	⊕OOO VERY LOW	CRITICAL

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist*
2 *2 Number of events <150*
3

Table 13: Clinical evidence profile for proportion of positive antibody tests in patients with a history of status epilepticus

Quality assessment						Number of patients			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Total	Total number of antibody positive (%)	Quality	Importance
Proportion of positive antibody tests (any) in patients with convulsive status epilepticus									
1 (Atmaca 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	12	3/12 (25)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests (any) in patients with non-convulsive status epilepticus									
1 (Atmaca 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	6	2/6 (33)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests (any) in patients with epilepsia partialis continua									
1 (Atmaca 2017)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	4	0/4 (0)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests (any) in patients with a history of status epilepticus									
1 (Tekturk 2018)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	9	0/9 (0)	⊕OOO VERY LOW	CRITICAL
Proportion of positive antibody tests (any) in patients with status epilepticus as a presenting feature									
1 (Wright 2016)	Observational study	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	11	2/11 (19)	⊕OOO VERY LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS checklist
2 Number of events <150

1

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: In people with epilepsy, who should have antibody testing?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: In people with epilepsy, who should have antibody testing?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: In people with epilepsy, who should have antibody testing?

No evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: In people with epilepsy, who should have antibody testing?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded studies for review question: In people with epilepsy, who should have 3 antibody testing?

4 Clinical studies

5 **Table 14: Excluded studies and reasons for their exclusion**

Excluded studies - Antibody testing	
Study	**Reason for Exclusion**
Cavus, I., Romanyshyn, J. C., Kennard, J. T., Farooque, P., Williamson, A., Eid, T., Spencer, S. S., Duckrow, R., Dziura, J., Spencer, D. D., Elevated basal glutamate and unchanged glutamine and GABA in refractory epilepsy: Microdialysis study of 79 patients at the yale epilepsy surgery program, Annals of neurology, 80, 35-45, 2016	Outcomes do not meet inclusion criteria - reported levels of GABA in epileptogenic and nonepiloptegic sites
Daif, A., Anti-glutamic acid decarboxylase 65 antibody associated epilepsy, Clinical Neurophysiology, 129 (Supplement 1), e68, 2018	Conference abstract
De Bruijn, M. A. A. M., Thijs, R. D., Majoie, H. J. M., Rouhl, R. P. W., Van Asseldonk, J. A. E., Van Donselaar, C., Leijten, F. S. S., Wirtz, P. W., Bastiaansen, A. E. M., Schreurs, M. W. J., Sillevis Smitt, P. A. E., Titulaer, M. J., Neuronal antibodies in a prospective, multicenter cohort of patients with focal epilepsy of unknown origin, Epilepsia, 59, S4-S5, 2018	Conference abstract
Dubey, D., Alqallaf, A., Hays, R., Freeman, M., Chen, K., Ding, K., Agostini, M., Vernino, S., Neurological Autoantibody prevalence in epilepsy of unknown etiology-ape study, Neurology, 88, 2017	Conference abstract
Dubey, D., Hays, R., Alqallaf, A., Freeman, M., Chen, K., Ding, K., Agostini, M., Vernino, S., Evaluating the prevalence of neurological autoantibodies among patients with epilepsy of unknown etiology: Ongoing prospective study, Neurology, 86, 2016	Conference abstract
Falip, M., Rodriguez-Bel, L., Castaner, S., Miro, J., Jaraba, S., Mora, J., Bas, J., Carreno, M., Musicogenic reflex seizures in epilepsy with glutamic acid decarbocylase antibodies, Acta Neurologica Scandinavica, 137, 272-276, 2018	Study design does not meet inclusion criteria - case series
Falip, M., Rodriguez-Bel, L., Castaner, S., Sala-Padro, J., Miro, J., Jaraba, S., Casasnovas, C., Morandeira, F., Berdejo, J., Carreno, M., Hippocampus and insula are targets in epileptic patients with glutamic acid decarboxylase antibodies, Frontiers in Neurology, 10 (JAN) (no pagination), 2019	Exposure does not meet inclusion criteria - study included only patients with high GAD antibody
Garcia-Tarodo, S., Datta, A. N., Ramelli, G. P., Marechal-Rouiller, F., Bien, C. G., Korff, C. M.,	Study design does not meet inclusion criteria - reported antibodies in mixed population, but subgroup analysis for epilepsy was not reported

Excluded studies - Antibody testing	
Circulating neural antibodies in unselected children with new-onset seizures, European Journal of Paediatric Neurology, 22, 396-403, 2018	
Gupta, S., Jayalakshmi, S., Yada, P. K., Surath, M., Clinical characteristics and outcome in autoimmune epilepsy from a tertiary care centre of South India, Journal of the Neurological Sciences, 381, 79-80, 2017	Conference abstract
Jehi, L., Searching for autoimmune epilepsy: Why, where, and when?, Epilepsy currents, 17, 363-364, 2017	Commentary
Karaaslan, Z., Ekizoglu, E., Tekturk, P., Erdag, E., Tuzun, E., Bebek, N., Gurses, C., Baykan, B., Investigation of neuronal auto-antibodies in systemic lupus erythematosus patients with epilepsy, Epilepsy Research, 129, 132-137, 2017	Population does not meet inclusion criteria - diagnosis of epilepsy was not confirmed
Liimatainen, S., Honnorat, J., Pittock, S. J., McKeon, A., Manto, M., Radtke, J. R., Hampe, C. S., GAD65 autoantibody characteristics in patients with co-occurring type 1 diabetes and epilepsy may help identify underlying epilepsy etiologies, Orphanet Journal of Rare Diseases, 13, 55, 2018	Study design does not meet inclusion criteria - reported GAD65Ab titer in mixed population, but subgroup analysis for epilepsy was not reported
Matricardi, S., Pappalardo, I., Freri, E., Ragona, F., Didato, G., Andreetta, F., Franceschetti, S., Nardocci, N., Pastori, C., Villani, F., Granata, T., Autoimmune epilepsy: Key findings to identify a potentially treatable disease, Epilepsia, 58, S24, 2017	Conference abstract
McKnight, K., Jiang, Y., Hart, Y., Cavey, A., Wroe, S., Blank, M., Shoenfeld, Y., Vincent, A., Palace, J., Lang, B., Serum antibodies in epilepsy and seizure-associated disorders, Neurology, 65, 1730-6, 2005	Study design does not meet inclusion criteria - reported antibodies in mixed population, but subgroup analysis for epilepsy was not reported
Ozen Aydin, C., Velioglu, S., Gazioglu, S., Tuzun, E., Neuronal antibodies in epilepsy patients with refractory seizures, Epilepsia, 58 (Supplement 5), S87, 2017	Conference abstract
Ravindar, G., Jayalakhshmi, S., Yada, P. K., Varalakhshmi, E. A., Mohandas, S., Clinical features and outcome of autoimmune epilepsies, Annals of Indian Academy of Neurology, 19, S92, 2016	Conference abstract
Sokol, D. K., McIntyre, J. A., Wagenknecht, D. R., Dropcho, E. J., Patel, H., Salanova, V., da Costa, G., Antiphospholipid and glutamic acid decarboxylase antibodies in patients with focal epilepsy, Neurology, 62, 517-8, 2004	Conference abstract
Striano, Pasquale, Perruolo, Giuseppe, Errichiello, Luca, Formisano, Pietro, Beguinot, Francesco, Zara, Federico, Striano, Salvatore, Glutamic acid decarboxylase antibodies in idiopathic generalized epilepsy and type 1 diabetes, Annals of neurology, 63, 127-8, 2008	Study design does not meet the inclusion criteria - case series.
Symonds, J., Vincent, A., Ellis, R., Williams, N., Lang, B., McClellan, A., Kirkpatrick, M., Jollands,	Conference abstract

Excluded studies - Antibody testing	
A., O'Regan, M., Macleod, S., et al.,, A prospective whole scottish population study of genetic and immune causes of epilepsy and complex febrile seizures in children under 3 years of age: the genetic and autoimmune childhood epilepsy (GACE) study, Epilepsia. Conference: 12th european congress on epileptology. Czech republic. Conference start: 20160911. Conference end: 20160915, 57, 30, 2016	
Umemura, Y., Ronan, L., VGKC autoimmunity: Are we missing patients who can benefit from immunotherapy?, Neuro-oncology, 15, 2013	Conference abstract
Vanli-Yavuz, E. N., Tuzun, E., Ulusoy, C., Ekizoglu, E., Baysal Kirac, L., Bebek, N., Gurses, C., Gokyigit, A., Baykan, B., Investigation of neuronal auto-antibodies in mesial temporal lobe epilepsy with hippocampal sclerosis, Epilepsia, 1), 190-191, 2015	Conference abstract
Wong, M. C. M., Arora, R., Phenotype of children with epilepsy and type 1 diabetes. A case series and study of anti-GAD antibody status, European Journal of Paediatric Neurology, 1), S28, 2015	Conference abstract
Wright, S. K., Jol-Van Der Zijde, C. M., Van Tol, M. J. D., Waters, P., Lang, B., Brouwer, O. F., Vincent, A., Epilepsy and the immune system " is there antibody there?", Epilepsy Currents, 1), 348, 2013	Conference abstract
Wright, S., Geerts, A. T., Jol-Van Der Zijde, C. M., Jacobson, L., Lang, B., Waters, P., Van Tol, M. J. D., Stroink, H., Neuteboom, R. F., Brouwer, O. F., Vincent, A., Neuronal antibodies in paediatric epilepsy: Clinical features and long-term outcomes, Epilepsia, 1), 252-253, 2015	Conference abstract
Wright, S., Jol-Van Der Zijde, C. M., Van Tol, M. J. D., Waters, P., Lang, B., Brouwer, O. F., Vincent, A., Epilepsy and the immune system "... is there antibody there?, Epilepsia, 5), 228-229, 2012	Conference abstract
Yarraguntla, K., Suchdev, K., Ibrahim, M., Shah, A., Relevance of serial anti-gad titers in relation to seizure frequency in autoimmune epilepsy (AIE): An observational study, Neurology, 90, 2018	Conference abstract
Yeo, T., Chen, Z., Yong, K. P., Wong, P. Y. W., Chai, J. Y. H., Tan, K., Distinction between anti-VGKC-complex seropositive patients with and without anti-LGI1/CASPR2 antibodies, Journal of the Neurological Sciences, 391, 64-71, 2018	Population does not meet the inclusion criteria - no reference to participants with epilepsy.

1 Economic studies

2 A global search of economic evidence was undertaken for all review questions in this guide-
3 line. See Supplement 2 for further information.

4

Appendix L – Research recommendations

Research recommendations for review question: In people with epilepsy, who should have antibody testing?

Research question

What immunomodulation strategies are effective in people with defined autoimmune epilepsy syndromes?

Why this is important

There have been reports of association of specific anti-neuronal antibodies with epilepsies, so-called autoimmune epilepsies. The significance of these antibodies is uncertain as in some cases they may be an epiphenomenon related to presentation of antigens secondary to tissue destruction in the central nervous system or elsewhere. Should such antibodies become clearly associated with a particular epileptic syndrome, treatment involving immunosuppression may be therapeutic. The committee considered that further research in this field should concentrate on defining the situations in which there was a clear association between particular antibodies and clinical syndromes, so that the pathogenesis could be more clearly defined, and treatment options explored. Once the association has been made, determining whether or not the antibodies are causative is difficult to do in humans and requires laboratory research using animal and cell models. Therefore, the focus of the research recommendation is on the next stage of assessing whether immunosuppression is beneficial.

Table 15: Research recommendation rationale

Research question	**What immunomodulation strategies are effective in people with defined autoimmune epilepsy syndromes?**
Why is this needed	
Importance to 'patients' or the population	It is plausible that some epilepsy syndromes are provoked by autoimmune processes, but to date it has not been able to demonstrate this. If it proves to be the case, immunosuppressive treatment may alter the prognosis of such conditions.
Relevance to NICE guidance	Knowledge about immunological triggering of epilepsy may have a material impact on diagnosis and treatment of some epilepsies.
Relevance to the NHS	Immune-mediated disorders require specialist immunosuppressive treatment to control the disease and improve prognosis.
National priorities	N/A
Current evidence base	Several studies provide evidence of the presence of anti-neuronal antibodies in people with epilepsy, but the specificity and significance of these findings remains unclear
Equality	N/A
Feasibility	Demonstration of an association of a specified epilepsy syndrome with the presence of circulating antibodies to an antigen present in the central nervous system is feasible, but the specificity and sensitivity of any association would subsequently have to be confirmed independently before investigation of an underlying pathophysiological process.

Research question	What immunomodulation strategies are effective in people with defined autoimmune epilepsy syndromes?
Other comments	There are many potential antigenic targets for candidate antibodies, and any association between an epilepsy syndrome and the presence of an antibody may be non-specific or an epiphenomenon (for example related to epilepsy- associated neuronal damage).

N/A: not applicable

Table 16: Research recommendation modified PICO table

Criterion	Explanation
Population	People with defined autoimmune epilepsy syndromes
Intervention	Immunomodulation strategies, including: • Steroids • Rituximab • IVIG • Plasmapheresis • Specific targeted therapies to pathogenic antibodies
Comparator	• No treatment • Placebo • Combinations of the above
Outcomes	• Mortality • Quality of life • Resolution of epilepsy • Resolution of encephalopathy • Relapse/recurrence
Study design	Randomised controlled trial
Timeframe	Not specified
Additional information	N/A

IVIG: Intravenous immunoglobulin; N/A: not applicable