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Psychiatric symptoms in anti glutamic acid decarboxylase associated limbic encephalitis in adults: a systematic review

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1 **TITLE PAGE**

2
3 **PSYCHIATRIC SYMPTOMS IN ANTI GLUTAMIC ACID DECARBOXYLASE**
4 **ASSOCIATED LIMBIC ENCEPHALITIS IN ADULTS: A SYSTEMATIC REVIEW.**

5
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36

37 ABSTRACT

38
39
40 Autoimmune Limbic Encephalitis (LE) is a relatively new category of immune-mediated diseases
41 with a wide range of neuropsychiatric symptoms. LE associated with Glutamic Acid
42 Decarboxylase (GAD) antibodies is difficult to diagnose due to its possible atypical presentation
43 with neuropsychiatric and behavioral features. We performed a systemic review of literature and
44 retrieved 21 cases of anti GAD-associated LE with neuropsychiatric signs. Median age at onset
45 was 27 years with a female predominance (81.0%) and median diagnostic delay 6 months.
46 Clinical presentation included typical LE symptoms such as anterograde amnesia (95.2%) and
47 temporal lobe or tonico-clonic seizures (95.2%). Psychiatric symptoms were described in 61.9%
48 of patients, presenting as anxiety, depressive symptoms, apathy and behavioral changes. Extra-
49 limbic symptoms were present in 14.3% of patients. No neoplasia associated was found. Some
50 patients had poor epileptic, cognitive and psychiatric outcomes requiring prolonged
51 immunosuppressive treatment. The description of the neuropsychiatric spectrum of anti-GAD LE
52 and its specificities aims to improve our understanding of this entity, and may lead to earlier
53 diagnosis as well as better outcome.

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60 Key words: encephalitis; limbic encephalitis; glutamic acid decarboxylase; GAD; neuronal
61 antibodies; neuropsychiatry

62 INTRODUCTION

63 Limbic Encephalitis (LE) is a form of encephalitis involving the median temporal lobes, the
64 amygdala and, less frequently, the fronto-basal and insular lobes, which may result from a viral
65 infection (*e.g.*, herpes simplex encephalitis) or from an autoimmune condition (1).

66 Clinical criteria for the diagnosis of autoimmune LE have recently been established (2). Several
67 autoantibodies with a specific tropism towards the limbic structures have been identified and
68 represent helpful markers for the diagnosis of LE (2). These autoantibodies can be directed to
69 intracellular neuronal antigens (*e.g.* onconeural antibodies Hu (3), collapsing response-mediator
70 protein-5 (CV2/CRMP5) (4), Ma2 (5) and amphiphysin (6)) or to cell-surface antigens (*e.g.* *N*-
71 methyl-D-aspartate receptor (NMDAR) (7) Leucine-rich glioma inactivated-1 (LGI1)(8),
72 Contactin-associated protein-like-2 (Caspr2) (9), Alpha-amino-3-hydroxy-5-methylisoxazol-4-
73 propionate Receptor (AMPA) (10), Gamma amino butyric acid (GABA_A, GABA_B) (11,12)). In
74 a proportion of cases, which depends on antibody type, the autoimmune process is triggered by
75 the presence of a tumor (paraneoplastic LE) (13), while in the remaining cases, autoimmunity
76 follows an infection or another unidentified trigger (idiopathic LE). Onconeural antibodies are
77 almost invariably associated with cancer while cell-surface antibodies are associated with cancer
78 in a proportion of cases variable from 10 to 80% (14). Not uncommonly, despite a presumed
79 autoimmune aetiology, no autoantibody is detected (seronegative LE) (15).

80 Over the last decade, autoimmune LE associated with antibodies to Glutamic Acid
81 Decarboxylase (GAD) has been increasingly reported (16). GAD is an intracellular enzyme
82 expressed in pancreatic islet cells and in neurons (17). This enzyme catalyses the decarboxylation
83 of glutamate to gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter within
84 the central nervous system. Anti-GAD antibodies appear to cause an imbalance resulting in
85 outweighing of excitatory neurotransmitters, leading to neuronal hyperexcitability (18).

86 Cases of LE associated with anti-GAD antibodies have been described since 1998 (19). The core
87 symptoms of anti-GAD LE include behavioral disturbances, seizures, and memory impairment,
88 reflecting a temporal lobe dysfunction. The last few years, the spectrum of symptoms associated
89 with anti-GAD LE has broadened with multiple cases described as having atypical clinical
90 features, such as psychiatric presentation and chronic course. In these patients, the diagnosis of
91 autoimmune encephalitis may have been overlooked and have been reached when permanent
92 damage was already set (20), explaining the poor response to immunotherapy (21).

93 Besides limbic encephalitis, anti-GAD antibodies have been associated with other neurological
94 syndromes including cerebellar ataxia, Stiff-Person Syndrome (SPS) and Progressive
95 Encephalomyelitis with Rigidity and Myoclonus (PERM) (22–24). High serum titers of anti-
96 GAD antibodies (>1000 UI/ml) have been also detected in some extra-neurological disorders,
97 including diabetes mellitus (DM) (25).

98 The aim of this review of the literature is (i) to provide a detailed description of the clinical
99 presentation associated with anti-GAD LE, (ii) to raise awareness on psychiatric clinical
100 presentations and (iii) to provide clues to suspect and test for anti-GAD antibodies.

101

102 REVIEW

103

104 **Methods**

105

106 This systematic review conforms to the Preferred Reporting Items for Systematic Reviews and
107 Meta-Analysis (PRISMA) guidelines (26).

108 Literature was systematically searched for adult cases reports or cases serie of LE with positive
109 anti-GAD antibodies in serum and/or CSF, matching the criteria for “definite autoimmune LE”

110 according to the definition of Graus *et al*, 2016 (2) (**Table 1**). The research was conducted on
111 Medline and PubMed for cases published in English from 1998 to 2019, using combinations of
112 the following keywords: “encephalitis” and “limbic encephalitis”, and “glutamic acid
113 decarboxylase antibodies”, “GAD 65”, “GAD 67” and “GAD”. We cross-checked reference lists
114 from retrieved publications in order to identify other potentially relevant articles. After exclusion
115 of duplicates, 67 original case reports or series of cases were screened and 60 full-text articles in
116 English were assessed for eligibility. We excluded pediatric cases (<14 years of age), cases that
117 did not fit the criteria for LE, LE cases with other antibodies associated with anti-GAD or with an
118 associated diagnosis of infectious encephalitis, cases that did not received a final diagnosis of LE
119 associated with anti-GAD. After selection, 19 articles were included, describing 21 original cases
120 (27–44). When a clinical symptom was not described, we assumed it was not present. When
121 paraclinical information was not otherwise specified, we considered the data as not available. We
122 managed to contact two authors to confirm accuracy of the clinical description of cases and to
123 obtain more information.

124 To be noted, the terms “behavioral disturbance/changes” could not be properly differentiated
125 from psychiatric symptoms *per se* due to the lack of details on behavioral symptoms available in
126 most of the case reports reviewed. Nonetheless, we considered symptoms such as apathy or
127 stereotypies on a dimensional approach as a behavioral disturbance. Psychiatric symptoms were
128 qualified as such when the symptoms description was unambiguous in the case reports, and used
129 in a categorical approach (use of psychiatric scale, clinical assessment by a trained
130 psychiatrist...).

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137 **Results**
138
139 **Clinical characteristics**
140
141 The clinical and paraclinical features of the 21 patients identified from our review are presented
142 in **Table 2**. All patients but one were Caucasian. The median age at the time of disease onset was
143 27 years, ranging from 14 to 56 years, with a sharp female predominance (81.0%, n=17). One-
144 third of patients (n=7) had a history of concomitant or prior autoimmune disorder: 23.8% (n=5)
145 had DM and 14.3% (n=3) dysthyroidism. Isolated biological abnormalities (positive anti-thyroid
146 antibodies) were found in 23.8% of patients (n=5).
147 Diagnostic delay ranged from one week to seven years, with a median of six months. Clinical
148 presentation included typical symptoms of LE such as anterograde amnesia (95.2%, n=20),
149 temporal lobe seizures (95.2%, n=20) or tonico-clonic seizures (14.3%, n=3). Formal
150 neuropsychometric assessment was available for 66.7 % of patients (n=12). Recent episodic
151 memory deficit was reported in 66.7% (n=14), in verbal and figural modalities; short-term
152 memory deficit in 23.8% (n=5). Impairment of executive function was reported in 23.8% (n=5).
153 No language impairment was observed. Neurocognitive profiles are detailed **Table 3**.
154 Temporal seizures had variable clinical presentation, ranging from somatic symptoms (nausea,
155 palpitations, flushes) to sensory distortions (hallucinations -auditory, visual, olfactory, gustatory,
156 tactile-; visual distortions -macropsia, micropsia-, synesthesia), paramnesic phenomena (“déjà-
157 vu” phenomenon), dissociative phenomena (depersonalization, derealization, heautoscopy) and
158 emotional manifestations (fear, anxiety, dysphoric or euphoric feelings). Psychiatric symptoms
159 were present in 61.9% of patients (n=13), including mood disorder (33.3%, n=7), anxiety
160 disorder (28.6%, n=6), and behavioral changes (33.3%, n=7) (**Table 4**). No significant familial or

161 personal history of psychiatric disorder was described. Specific evaluation by a psychiatrist was
162 explicitly mentioned for two patients and only one patient was screened and monitored for
163 depression with a specific scale (Beck Depression Inventory). Mood disorders consisted in
164 depressed mood (n=7) and emotional instability (n=2). Suicidal ideation was reported in Patient
165 N°11 (35). Behavioral changes reported were apathy (n=3), irritability (n=1) and bizarre
166 behavior/personality changes (n=4). Confabulations were reported for one patient, Patient N°13
167 (37). In 3 patients (Patient n°7 (31), Patient n°16 (40) and Patient N°17 (45)), psychiatric
168 symptoms were probable inaugural signs of LE, preceding epileptic and cognitive symptoms of
169 LE by several months. In Patient N°17 (45), the depressed mood, significant emotional
170 instability, and bewilderment associated with the cognitive impairment lead to initial diagnosis of
171 burn-out, psychosomatic condition, amnesic dissociation and depression by various practitioners.
172 Patient N°11 (35) presented *de novo* psychiatric symptoms after diagnosis of LE, along with the
173 worsening of cognitive symptoms after first-line treatment. During the evolution of the disease,
174 Patient N°16 (40) presented with behavioral symptoms that required admission and care in a
175 psychiatric ward.

176 Only 14.3% of patients (n=3) had signs and symptoms of extra-limbic involvement, consisting of
177 cerebellar signs (nystagmus and/or ataxia), compatible with cerebellar ataxia associated with anti-
178 GAD antibodies. Patient N°19 (43) presented with rigidity and spasms of limbs and continued
179 motor unit activity in electromyography, consistent with a concomitant diagnosis of Stiff-Person
180 syndrome.

181

182 **Investigations**

183

184 GAD antibodies were tested in serum in all cases and in CSF in 15 cases. Immunohistochemistry
185 immunoblot, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) were
186 used. GAD antibodies titer in serum ranged from 72 UI/mL to 463 000 UI/mL (median value:
187 2000 UI/mL). GAD antibodies titer in CSF was available in 15 patients and ranged from 46
188 UI/mL to more than 15 400 UI/mL (median value: 120 UI/mL). The ratio between CSF and
189 serum antibodies titer was reported for 9 patients and ranged from 0.003 to 0.88 (median value:
190 0.35). GAD antibody index was available for 5 patients with a median value of 35,5 (normal
191 range <7), demonstrating an active synthesis of anti-GAD antibodies in CSF. Intracellular and
192 cell-surface neuronal antibodies other than GAD were tested and excluded in 20 out of 21
193 patients.

194 All patients displayed MRI alterations involving the amygdala and the median temporal lobe. Up
195 to 81.0% of patients (n=17) showed bilateral abnormalities and 19.0% (n=4) only unilateral
196 involvement of the temporal lobe. Hypersignals were described in 100% of patients (n=21) and
197 significant swelling was observed in 28.6% of patients (n=6).

198 EEG was available for 20 out of 21 patients, revealing slow or epileptic abnormalities in all
199 cases. In Patient N°15 (39), temporal seizures and abnormal EEG findings appeared at relapse,
200 after two years of evolution. Fifty-seven % (n=12) had an ictal EEG showing electroclinical
201 temporal seizures and 28.6% (n=6) presented with interictal epileptiform discharges or temporal
202 slow waves. Generalized slow waves were seen in one patient (Patient N°9 (33)). Complex
203 partial temporal status epilepticus with temporal onset was found for two patients (Patient N°3
204 (28) and Patient N°11 (35)).

205 CSF analysis was available for all patients. Most patients had normal cell count and protein
206 levels. Mild pleocytosis (from 5 to 9 elements/mm³) was found in 23.8% of patients (n=5) and
207 high CSF protein level in a single patient (Patient N°15 (39)). CSF-specific oligoclonal bands

208 were instead detected in 66.7% of patients (n=14). To be noted, three patients had no oligoclonal
209 bands despite having positive anti-GAD antibodies in the CSF.

210 The search for an occult neoplasm by total-body Computerized Tomography (CT) and/or
211 Positron Emission Tomography-CT (PET-CT) was performed in 20 of 21 patients and was
212 negative in all cases.

213

214 **Treatment**

215

216 All patients received at least one line of immunotherapy. First-line treatment consisted of
217 corticosteroids (n=15), intravenous immunoglobulin (n=10), plasma exchange (n=1) and
218 Rituximab (n=1), used alone (n=11, 52.4%) or in combination (n=10, 47.6%).

219 Despite first-line treatment, 61.9% of patients (n=13) needed a second-line of immunotherapy
220 due to the lack of clinical improvement, and 14.3% of patients (n=3) even a third line of
221 treatment. Second and third lines of treatment consisted of plasma exchange (n=4), intravenous
222 immunoglobulins (n=3), Azathioprine (n=2) and Rituximab (n=1). Patient n°16 (40) was treated
223 with Basiliximab (46), an anti-Interleukine 2 monoclonal antibody.

224 Long-term immunosuppression was undertaken in 28.6% of patients (n=6), using Mycophenolate
225 Mofetil (19.0%, n=4), Azathioprine (14.3%, n=3) and Cyclophosphamide (n=1). All patients
226 were given antiepileptic drugs (even in the absence of clinical seizure). The most commonly
227 administered antiepileptic drugs included Levetiracetam (n=10) and Carbamazepine (n=6). Some
228 patients needed up to four medications to obtain seizure control. Four patients were started on
229 antidepressant and Patient N°17 (40) received Risperidone to treat the behavioral symptoms.

230

231 **Follow-up and outcome**

232

233 The median follow-up was 1.5 years (range: 3 months - 5 years). All in all, 71.4 % of patients

234 (n=15) experienced some clinical improvement following first-line treatment, after a mean delay
235 of 2 ± 1.4 months from immunotherapy initiation; 9.5% (n=2) responded to second-line treatment,
236 while only one patient responded to third-line treatment. Remission was more frequent in patients
237 receiving long-course immunosuppressants: 85.7% of patients who received immunosuppressant
238 treatment (n=6/7) showed an improvement whereas only 57.1% of patients improved under
239 immunotherapy alone (n=8/14). Eleven out of 21 patients experienced relapses (52.4%) after a
240 mean period of 6.15 ± 5.7 months from diagnosis. Relapse was characterized by reappearance of
241 symptoms in all but one case (Patient n°15 (39)) who experienced *de novo* seizure activity.
242 At last follow-up, 90.5% of patients (n=19) were improved compared to the peak of disease
243 severity. Cognitive improvement was reported in 81.0% of patients (n=17). Four patients (19.0%)
244 were described as free of cognitive symptoms. Eleven patients were reassessed with
245 neuropsychometric tests. Seven patients showed improvement (n=7/11, 63.6%): verbal and
246 figural memory improvement was described in 6 patients. Partial recovery of autobiographic
247 memory was reported for one. Four patients did not show improvement on formal
248 neuropsychometric testing (n=4/11, 36.4%). Following the introduction of antiepileptic
249 treatment, 6 out of 20 patients who had seizures during the acute phase of disease became
250 seizure-free (30.0%) while 12 additional patients experienced a significant reduction in seizure
251 frequency (57.1%). Psychiatric outcome was explicitly reported for 4 patients and described as
252 positive in all cases. Patient N°17 (45) significantly improved on Beck Depression Inventory
253 after 7 months of well-conducted immunotherapy and antidepressant medication. Control brain
254 MRI was available for 11 patients, showing a regression of swelling and/or temporal
255 hyperintensity in 7 cases. Subsequent hippocampal atrophy appeared unequivocally in 2 cases on
256 control brain MRI after 8 months (Patient N°3 (28)) and 15 months (Patient N°12 (36)) of follow-
257 up.

258 Twelve patients had repeated anti-GAD antibodies titer measure in serum after treatment. Among
259 them, 66.7% (n=8/12) showed a decrease in antibody titers along with a significant clinical
260 improvement. The remaining 4 patients had stable serum anti-GAD antibodies titer, despite
261 significant clinical improvement. Three patients had repeated anti-GAD antibodies titer in the
262 CSF. A significant decrease was noticed in two cases, along with a significant clinical
263 improvement. Patient N°16 (40) had stable anti-GAD antibodies titer despite clinical
264 improvement. Four patients repeated anti-GAD antibodies titer in serum at the time of relapse,
265 showing a titer increase in all cases.

266

267 **DISCUSSION**

268

269 Anti-GAD LE appears to be associated to peculiar clinical features compared to other types of
270 autoimmune LE. Indeed, although all cases reported in our review fulfilled the criteria of
271 autoimmune LE, as defined by Graus *et al*, 2016 (2) (**Table 2**), delay to diagnosis was extended.
272 Prominent psychiatric presentation is in fact possibly associated to a higher risk of misdiagnosis.
273 In a recent epidemiologic study, anti-GAD antibodies were the third antibodies in terms of
274 frequency after anti-NMDA and anti-MOG antibodies (16). However, less than 100 case reports
275 of anti-GAD LE in adults have been published so far in the literature, suggesting that anti-GAD
276 LE is probably an underdiagnosed condition.

277

278 **Hallmarks of limbic involvement.** Seizure and long-term memory loss represent the hallmarks
279 of LE. Temporal amnesic syndrome is characterized by impairment of verbal and visual memory,
280 with loss of storage, consolidation and learning. The cognitive dysfunction seen in mood and
281 anxiety spectrum disorders is instead characterized by impairment of executive functions

282 (working memory, processing speed and verbal fluency) (47–49) with relative sparing of verbal
283 and visual episodic memory. Brain MRI always showed structural abnormalities, even though
284 sometimes discreet. Epilepsy appears as a core symptom of GAD antibodies associated LE
285 (100% abnormal EEG) and thus should always be screened for and treated, as it may participate
286 to the severity and/or to the persistence of cognitive and psychiatric symptoms.

287 **Psychiatric symptoms are prominent.** Psychiatric symptoms are common in patients with LE
288 (50) and auto-immune LE are increasingly recognised as a key differential diagnosis for acute
289 psychiatric disturbance. Psychiatric manifestations in specific auto-antibody syndromes have
290 been well described in the literature: anti-NMDA receptors antibodies LE patients are known to
291 present with psychotic symptoms (delusional thoughts and hallucinations) (51,52). Depression,
292 anxiety and hallucinations are commonly found in anti-HU associated LE (3).

293 In our review, more than 60% of patients presented with psychiatric symptoms which, in some
294 cases, appeared up to several months prior to seizures and cognitive symptoms. In a recent review
295 of 58 cases of anti-GAD associated LE, including 26 adults and 21 children, psychiatric
296 symptoms were found in only 28% of patients (mainly depression, behavioral and personality
297 changes) (53). The difference in prevalence in comparison to our review may be due to an
298 overlook of psychiatric symptoms in the presence of other symptoms. In our patients, the absence
299 of psychiatric history prior to LE onset, the appearance of psychiatric symptoms during relapse in
300 one patient (Patient N°11, (35)), and the mostly positive outcome of those symptoms after
301 immunotherapy support the imputability of anti-GAD antibodies in the psychiatric features. Anti-
302 GAD antibodies have also been reported to be more frequent in patients suffering from bipolar
303 disorder compared to healthy controls (11.3% versus 2.6%, $p=0.002$ (54)). As prompt recognition
304 of an autoimmune etiology can lead to effective treatment, identifying psychiatric features as an
305 element raising suspicion for autoimmunity is of importance and patients should be assessed for

306 associated neurological symptoms. It is likely that, in some of the patients initially assessed by a
307 psychiatrist, neurological symptoms referring to a possible diagnosis of encephalitis might have
308 been overlooked because of poor screening for subtle neurological and cognitive symptoms.

309
310 **Female sex predominance and autoimmune comorbidity is frequent.** Anti-GAD associated
311 LE affects mostly young women (85% in our review), similarly to anti-NMDA receptors
312 encephalitis (91% in a review of 100 patients by Dalmau *et al*, 2011 (7)). A systemic
313 autoimmune condition (DM, dysthyroidism) was frequent, suggesting that LE occurs in patients
314 with a vulnerability to autoimmune disorders.

315
316 **Symptoms are of long duration.** Delay in diagnosis is longer compared to other forms of LE.
317 LE anti-GAD may even be described as a chronic phenomenon. Median delay in diagnosis in our
318 review was 6 months compared to 1.5 months in anti-NMDA limbic encephalitis (55).

319
320 **Extralimbic neurological signs are often absent.** In this review, we did not find much overlap
321 with other neurological syndromes associated with anti-GAD antibodies. Only 15% of patients
322 (n=3) presented with cerebellar ataxia and one had manifestation of Stiff-Person syndrome,
323 ascertaining that LE is rarely associated with extralimbic involvement.

324
325 **Antibodies titer and clinical severity.** Literature states that the patients with neurologic
326 disorders show higher serum anti-GAD antibodies titer compared to patients with DM (56). To
327 that matter, the anti-GAD antibody index is usually elevated, suggesting intrathecal antibody
328 synthesis. Serum anti-GAD antibodies titer was lower in LE cases compared to the ones reported
329 in Stiff-Person syndrome and cerebellar ataxia (a mean of respectively 17 500 UI/mL and 16 737

330 UI/mL, in 22 and 17 patients, in the biggest cohort reported by Saiz *et al*, 2008(23)). It is still
331 unclear whether serum anti-GAD antibodies titer correlates with the disease severity. In 20% of
332 patients in the present review, anti-GAD antibodies titer decreased with clinical improvement and
333 increased at relapse. This result underpins that anti-GAD antibodies titer may be a useful marker
334 to monitor disease evolution.

335
336 **GAD-associated LE is rarely paraneoplastic.** None of the patients presented with an associated
337 tumor. Saiz *et al*, 2008 (23) and Ariño *et al*, 2015 (21) described 5 cases of paraneoplastic LE
338 associated with anti-GAD65 antibodies, associated with small cell lung cancer and older age at
339 diagnosis.

340
341 **Outcome under treatment is poor.** The mnemonic function outcome was globally poor, even after
342 the second-line (70% of patients) and third-line treatment (15%). Moreover, despite a large
343 number of antiepileptic drugs, a large proportion of patients (60%) was not seizure free. To date,
344 there are no specific recommendations for the treatment of anti-GAD LE. Corticosteroids, IVIg
345 and plasma exchange are all considered as suitable first-line options, although experts tend to
346 advise the use of Rituximab as a first line of treatment, especially in severely affected patients.

347
348 **Pathophysiology.** The question remains whether anti-GAD antibodies have a pathophysiological
349 role in relation to the neuropsychiatric symptoms or are only disease biomarkers. Although it
350 seems clear that altered GABAergic transmission represents the core pathophysiological
351 component involved (57,58), the exact mechanisms responsible for neuronal dysfunction in anti-
352 GAD associated LE and the possible direct pathogenicity of the antibodies remain debated. To
353 date, the pathogenicity of anti-GAD antibodies has not been unequivocally proven, either in Stiff-

354 Person syndrome (the most studied entity) or in other clinical presentations (59). There is a
355 prevalence of 6.5% of anti-GAD antibodies in other neurological disorders (including multiple
356 sclerosis) (60). This prevalence is close to the one found in general population (0.7-48% (61)),
357 which could indicate unspecific association with neurological disorders. However, compelling
358 arguments exist to establish an association between neurological manifestations and the presence
359 of anti-GAD antibodies. The detection of anti-GAD antibodies in CSF has only been reported in
360 patients presenting with neurological symptoms so far (23). Pathological study of three cases of
361 limbic encephalitis associated to anti-GAD antibodies showed hippocampal neuronal loss and
362 cytotoxic T cells apposition to target neurons, compatible with intra-cellular antigen
363 pathogenicity (62). In rat hippocampus, in controlled conditions, injection of human CSF
364 containing anti-GAD antibodies from patient with anti-GAD associated LE could induce
365 epileptic activity (63).

366 To the best of our knowledge, no specific study has been conducted on the pathogenicity of anti-
367 GAD antibodies on psychiatric and behavioral clinical presentations of LE. In this context, we
368 can only extrapolate its relation from other fields of fundamental and clinical research. In regard
369 to depression, although this disease is multifactorial, with different levels of explanation
370 (neurochemical, neuroendocrine, immunological...), associated structural and functional
371 abnormalities in the limbic-cortico-striato-pallido-thalamic pathway has been widely reported on
372 a functional and structural anatomical level (64). More interestingly, there is a high prevalence of
373 depression in patients with temporal lobe epilepsy, especially in women (65). Reduced cortical
374 thickness of the amygdala and hippocampus has been mentioned to better explain its
375 physiopathology (66). Regarding anxiety symptoms, these are the most common psychiatric
376 symptoms of temporal lobe epilepsy. The amygdala and hippocampus are part of a neuronal

377 network which dysfunction plays an important role in the generation of anxiety and
378 epileptogenesis and has been well-documented in numerous studies (67,68).

379 All compelled, we can presume a pathogenicity of anti-GAD antibodies on specific parts of the
380 limbic pathway, leading to various symptoms, from firstly isolated depression/anxiety to
381 cognitive and motor dysfunction, as well as intricated neuropsychiatric symptoms. It appears
382 complex to definitively conclude on the immune mechanisms responsible for neuronal
383 dysfunction and neuropsychiatric symptoms in GAD-antibodies associated LE, highlighting to
384 what extent GAD antibodies constitute a peculiar case among antibodies associated to
385 autoimmune encephalitis.

386

387 Limits

388

389 This review has its inherent limitations. We excluded cases without precise clinical description as
390 we focused our work on neurological and psychiatric symptoms. That might have brought a bias
391 in the characterization of the entity we aim to describe in this review. Clinical details were
392 sometimes unavailable and no standardized neurological and psychiatric evaluation were used. It
393 is likely that some of the non-reported symptoms were present in some patients. Vocabulary may
394 have differed from one article to another for the description of psychiatric features, leading to
395 different interpretations. Some patients may not have benefited from a proper psychiatric
396 evaluation by a trained psychiatrist. Therefore, mild psychiatric symptoms may have appeared of
397 minor importance compared to neurological symptoms such as seizure, and thus would have been
398 underreported. In regards to laboratory tests, antibodies assay was not performed in CSF for 30%
399 of patients. Measurement techniques were heterogeneous, including Enzyme Linked

400 ImmunoSorbent Assay (ELISA), Radio-immunoassay, and Immuno-Fluorescence, with different
401 thresholds for positivity in the different laboratories. Anti-GAD antibody index, reflecting the
402 intrathecal antibody synthesis, was available for only 45% of patients. The small sample size of
403 cohort warrants further caution about these conclusions. A confirmation bias cannot be excluded,
404 through overreporting of exceptional cases or of cases with better outcome. Larger cohort studies
405 including LE patients with other antibodies will allow to further characterize anti-GAD
406 associated LE and its specificities.

407 **CONCLUSION**

408
409 In this review of the literature, we described anti-GAD LE spectrum in adults and its hallmarks.
410 Anti-GAD LE appears to be a slowly-progressive condition associated with prominent
411 psychiatric symptoms such as anxiety, depression, apathy and behavioral changes, which can
412 initially represent the sole clinical manifestation of the disease. Young women with history of
413 autoimmune disorder and psychiatric symptoms should be promptly tested for anti-GAD
414 antibodies. Early diagnosis and immunotherapy initiation could possibly improve the outcome
415 associated with this condition, which to date is characterized by cognitive sequelae and risk for
416 relapse.

417

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422

423 **Conflict of interest**

424

425 The authors declare that they have no competing interest to disclose concerning this article.

426

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430

431 **Abbreviations**

432 CSF: Cerebro Spinal Fluid; CT: Computerized Tomography; DM Diabetes Melitus; EEG:

433 Electroencephalography; ELISA: Enzyme Linked Immuno-absorbant Assay; GABA: *Gamma-*

434 AminoButyric Acid; GAD: Glutamic Acid Decarboxylase; LE: limbic encephalitic; MRI:

435 Magnetic Resonance Imaging; NMDA: N-Methyl D Aspartate; SPS: Stiff Person Syndrome;

436 PET-CT: Positron Emission Tomography Computerized Tomography;

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Diagnostic criteria for definite autoimmune limbic encephalitis	
<i>Diagnosis can be made when all four of the following criteria have been met:</i>	
1.	Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2.	Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
3.	At least one of the following: <ul style="list-style-type: none"> • CSF pleocytosis (white blood cell count of more than five cells per mm³) • EEG with epileptic or slow-wave activity involving the temporal lobes
4.	Reasonable exclusion of alternative causes

Table 1. Diagnostic criteria for definite autoimmune limbic encephalitis according to Graus *et al*, 2016 (2)

Patient n°, publication	Sex, age (years old y. o.), evolution time (years y.)	Neurological symptoms	Psychiatric symptoms	MRI	CSF	Serum Anti-GAD Ab (UI/mL)	CSF Anti-GAD Ab (UI/mL)	Treatment -1 st line	Treatment- 2 nd and 3 rd Line	Length of follow-up (year y., month, mo.), outcome
1. Matá <i>et al.</i> , 2008 (27)	F, 14 y. o., 6 y.,	Temporal seizures, anterograde amnesia	None	Bilateral temporal hyperintensity	Intrathecal synthesis	87.5	54.1	Ig IV, IV steroids	PE	2 y., improvement, relapse
2. Matá <i>et al.</i> , 2008 (27)	F, 47 y. o., 0.5 y.	Temporal seizures, anterograde amnesia	Depression, anxiety	Bilateral temporal hyperintensity and swelling	Intrathecal synthesis	72	46	PE, IV steroids	0	5 y., improvement, relapse
3. Akman <i>et al.</i> , 2009 (28)	F, 16 y. o., 0.5 y.	Complex partial status epilepticus, anterograde amnesia, nystagmus, gait instability	None	Bilateral temporal hyperintensity	0	>300	> 300	IV steroids	Ig IV	1 y., improvement, relapse, hippocampal sclerosis
4. Blanc <i>et al.</i> , 2009 (29)	M, 30 y. o., 0 y.	Anterograde amnesia (MMSE 24/30)	None	Bilateral temporal hyperintensity	Intrathecal synthesis	463 000	NA	Ig IV, IV steroids	Mycophenolate Mofetil	2 y., improvement, relapse, improvement after 2 nd line
5. Saidha <i>et al.</i> , 2010 (30)	F, 22 y. o., 0.5 y.	Temporal seizures, anterograde amnesia (MMSE 27/30), confusion	None	Bilateral temporal hyperintensity and swelling	Intrathecal synthesis	> 1000	NA	Ig IV	Oral steroids, Mycophenolate Mofetil	2 y., improvement
6. Saidha <i>et al.</i> , 2010 (30)	F, 47 y. o., 1 y.	Temporal seizures, anterograde amnesia	None	Bilateral temporal hyperintensity and swelling	Intrathecal synthesis	> 1000	NA	Ig IV	Oral steroids, Azathioprine, Mycophenolate Mofetil	2 y., improvement
7. Cianci <i>et al.</i> , 2010 (31)	F, 27 y. o., 0 y.	Temporal seizures, anterograde amnesia and dysexecutive syndrome (MMSE 28/30)	Depression, anxiety	Bilateral temporal hyperintensity, asymmetric	Intrathecal synthesis	6000	120	IV steroids	Oral steroids	1 y., worsening
8. Finelli <i>et al.</i> , 2011 (32)	F, 53 y. o., 4 y.	Temporal seizures, anterograde amnesia (MMSE 28/30), nystagmus	Apathy	Left temporal hyperintensity	0	630	54.3	Ig IV	0	No follow-up
9. Sharma <i>et al.</i> , 2012 (33)	F, 22 y. o., 0 y.	Encephalopathy, anterograde amnesia	Behavioral changes	Bilateral temporal hyperintensity	0	Positive	NA	Ig IV, IV steroids	0	No follow-up, improvement
10. Lopez-Sublet <i>et al.</i> , 2012 (34)	F, 22 y. o., 5 y.	Temporal seizures, anterograde amnesia and dysexecutive syndrome	Depression, anxiety, behavioral changes, irritability	Bilateral temporal hyperintensity	Intrathecal synthesis	115	102	Ig IV,	0	8 mo., improvement
11. Mishra <i>et al.</i> , 2013 (35)	M, 15 y. o., 0.5 y.	Complex partial status epilepticus, tonico clonic seizures, anterograde amnesia	Depression, anxiety, suicidal ideation	Bilateral temporal hyperintensity, asymmetric	Pleocytosis (7/mm ³), intrathecal synthesis	Positive	Positive	Ig IV, oral steroids	Rituximab, Ig IV, oral steroids	1 y., improvement, relapse

12. García García <i>et al.</i> , 2013 (36)	F, 29 y. o., 0 y.	Temporal seizures, anterograde amnesia and dysexecutive syndrome (MMSE 24/30)	None	Bilateral temporal hyperintensity	Pleocytosis, intrathecal synthesis	Positive	Positive	Ig IV, Rituximab, Cyclophosphamide	Azathioprine	1 y., worsening, hippocampal sclerosis
13. Markakis <i>et al.</i> , 2014 (37)	F, 48 y. o., 2 y.	Agitation, temporal seizures, anterograde amnesia, confusion	Confabulation	Bilateral temporal hyperintensity and swelling	Pleocytosis (5/mm ³), intrathecal synthesis	37 500	15 400	IV steroids	PE, oral steroids	1 y., improvement
14. Farooqi <i>et al.</i> , 2014 (38)	F, 19 y. o., 5 y.	Temporal seizures, tonico-clonic seizures	None	Right temporal hyperintensity	0	115 900	NA	Oral steroids, Mycophenolate Mofetil	PE	1 mo., improvement, relapse
15. Van Ael <i>et al.</i> , 2015 (39)	F, 26 y. o., 0 y.	Temporal seizures, anterograde amnesia, confusion	None	Right temporal hyperintensity	Elevated CSF proteine, pleocytosis (7/mm ³), intrathecal synthesis	7900	NA	IV steroids	PE	2 y., improvement, relapse
16. Widman <i>et al.</i> , 2015 (40)	M, 25 y. o., 7 y.	Agitation, temporal seizures, anterograde amnesia, dysexecutive syndrome	Depression, behavioral changes	Bilateral temporal hyperintensity and swelling	Intrathecal synthesis	> 2000	Positive	IV steroids	Basiliximab	3y., improvement, relapse
17. Witt <i>et al.</i> , 2015 (45)	M, 35y.o., 0.5 y	Anterograde and retrograde memory deficit, suspicion temporal seizures	Depressed mood, emotional lability	Bilateral swelling , alteration of temporomesial structures	Intrathecal synthesis	>20000	Positive	IV steroids	0	2 y., improvement
18. Fauser <i>et al.</i> , 2015 (41)	F, 56 y. o., 4 y.	Temporal seizures, anterograde amnesia	Depression, anxiety, emotional lability	Right temporal hyperintensity	0	15 800	48	IV steroids	0	1 y., improvement
19. Sharma <i>et al.</i> , 2016 (43)	F, 30 y. o., 0 y.	Tonico-clonic seizures, anterograde amnesia, cerebellar syndrome, rigidity	Apathy	Bilateral temporal hyperintensity	0	Positive	Positive	Ig IV, Azathioprine	0	3 mo., improvement
20. Gardner <i>et al.</i> , 2016 (42)	F, 21 y. o., 0 y.	Temporal seizures, anterograde amnesia	Anxiety	Bilateral temporal hyperintensity	Pleocytosis (9/mm ³)	250	53	IV steroids, oral steroids	Ig IV, IV steroids	0 y., improvement, relapse at 3 and 6 mo.
21. Bougea <i>et al.</i> , 2017 (44)	F, 37 y. o., 0 y.	Temporal seizures, anterograde amnesia, confusion	Behavioral changes	Bilateral temporal hyperintensity	Intrathecal synthesis	42 500	15 400	PE, IV steroids	0	0 y., improvement

Table 2. Clinical characteristics, laboratory/imaging findings and treatments of the cases.

MMSE: Mini Mental State Examination; CSF: Cerebro Spinal Fluid; Ig IV: Intravenous Immunoglobulins; IV: Intravenous. PE: Plasmatic Exchanges. NA: Non available

Case N°, Publication	Modality of evaluation	Domains assessed (tests performed if specified)	Reported cognitive deficits at diagnosis	Evolution of cognition
1. Matà <i>et al</i> , 2008 (27)	Neuropsychometrical testing	Verbal memory, spatial memory (immediate and delayed recall)	Verbal memory, spatial memory	Improvement (clinical assessment)
2. Matà <i>et al</i> , 2008 (27)	Clinical assessment	Short-term verbal memory (3 words recall), general intellectual functioning	Short-term verbal memory (0/3 words recalled)	Initial improvement, relapse; no improvement at final follow-up
3. Akman <i>et al</i> , 2009 (28)	Clinical assessment	Academic functioning	Decline in academic functioning	Unchanged
4. Blanc <i>et al</i> , 2009 (29)	Neuropsychometrical testing	General intellectual ability (MMSE), verbal working memory (Forward and Backward Digit span), visuo-spatial (Complex Rey Figure copy)	Decline in general intellectual ability (MMSE: 24/30) Verbal memory	Improvement on verbal memory and visual memory
5. Saidha <i>et al</i> , 2010 (30)	Neuropsychometrical testing	General Intellectual ability (MMSE), multi-modal memory (RBMT)	Verbal, visual and spatial memory (RBMT: screening 2/12; total 6/24), (MMSE preserved: 27/30)	Improvement (normalization of RBMT)
6. Saidha <i>et al</i> , 2010 (30)	Neuropsychometrical testing	General Intellectual ability (MMSE), multi-modal memory (RBMT)	Verbal memory (RBMT: screening 7/12; total 16/24) (MMSE preserved: 28/30)	Improvement (improvement of RBMT score)
7. Cianci <i>et al</i> , 2010 (31)	Neuropsychometrical testing	Verbal memory (recall of a short story, WMS-III VPA), Visuo-spatial functions (Raven Colored Matrice), verbal fluencies	Verbal memory	Unchanged (neuropsychometrical testing)
8. Finelli <i>et al</i> , 2011 (32)	Clinical assessment	General intellectual ability (MMSE), semantic memory, language	Verbal memory, semantic memory, general intellectual ability preserved (MMSE: 28/30)	Unchanged
9. Sharma <i>et al</i> , 2012 (33)	Neuropsychometrical testing	General intellectual ability (MMSE), episodic memory, language	Decline in general intellectual ability, episodic memory	Improvement
10. Lopes-Sublet <i>et al</i> , 2012 (34)	Neuropsychometrical testing	General intellectual ability, multi-modal memory testing, executive functions	Decline in general intellectual ability, episodic memory, executive functions	Improvement (neuropsychometrical testing)
11. Mishra <i>et al</i> , 2013 (35)	Clinical assessment	General intellectual ability (MMSE), short-term and long-term episodic memory, procedural memory	Long-term episodic memory, mental slowing (general intellectual ability preserved, MOCA: 30/30)	Improvement after a relapse
12. García García <i>et al</i> , 2013 (36)	Neuropsychometrical testing	General intellectual ability (MMSE), memory (FCSRT, Digit span, Rey Complex Figure recall), executive functions (planning and decision-making, copy of Rey-Osterrieth Complex Figure)	Episodic memory, visual memory, executive functions	Improvement in visual memory and executive functions; no change in verbal memory test results
13. Markakis <i>et al</i> , 2014 (37)	Neuropsychometrical testing	Working memory, verbal memory, visual memory, language functions	Working memory, verbal memory, visual memory	Improvement in verbal and visual memory (neuropsychometrical testing)
14. Farooqi <i>et al</i> , 2014 (38)	Clinical assessment	General intellectual ability (MMSE), short-term memory	No decline (MMSE: 30/30)	No decline observed in course of disease
15. Van Ael <i>et al</i> , 2015 (39)	Clinical assessment	Short-term memory	Short-term memory	Improvement followed by relapse
16. Widman <i>et al</i> , 2015 (40)	Neuropsychometrical testing	Verbal memory (VLMT), figural memory (DCS-R), spatial memory (Maze test), executive functions (TMT A&B, written verbal fluency test, backward digit test)	Verbal memory, figural memory, executive functions	Following treatment and relapse: only improvement of verbal memory (decline of figural memory and executive functions)
17. Witt <i>et al</i> , 2015 (44)	Neuropsychometrical testing	Figural memory, working memory (VLMT 1), short-term verbal memory (VLMT 7), long-term memory (VLMT 8), executive functions	Figural memory, long-term memory, biographic memory	Decrease in verbal memory, recovery of biographical memory
18. Fauser <i>et al</i> , 2015 (41)	Neuropsychometrical testing	Episodic memory, figural memory, verbal memory, verbal fluency, executive functions (processing speed, divided and selective attention)	Episodic memory, verbal memory, figural memory	Figural & episodic memory: pathological; Verbal memory, verbal fluency: low average
19. Sharma <i>et al</i> , 2016 (43)	Clinical assessment	Immediate memory, short-term memory	Short-term memory	Improvement
20. Gardner <i>et al</i> , 2016 (42)	Clinical assessment	Short-term memory	Short-term memory	Multiple relapse of memory impairment
21. Bougea <i>et al</i> , 2017 (44)	Clinical assessment	Short term memory	Short-term memory	Improvement

Table 3. Neuropsychological profile at diagnosis and follow-up

MMSE: Mini Mental State Examination. RBMT: Rivermead Behavioral Memory Test. MOCA: Montreal Cognitive Assessment. VLMT: Verbal Learning and Memory Test. FCSRT: Free and Cued Selective Recall Test. DCS-R: Diagnosticum für CerebralSchädigung. TMT: Trail Making Test.

Case N°, Publication	Sex, age	Delay of psychiatric symptoms prior to the onset of the disease	Symptoms	Evaluation	Specific treatment	Outcome
1. Matà, <i>et al.</i> 2008 (27)	F, 47 y. o.	0 month	Mild depression	Clinical evaluation		Improvement
7. Cianci <i>et al.</i> , 2010 (31)	F, 27 y. o.	0 month	Depression, anxiety	Clinical evaluation	Antidepressants	No improvement
8. Finelli <i>et al.</i> , 2011 (32)	F, 57 y. o.	1 year	Apathy, behavioral changes	Clinical evaluation		No improvement
9. Sharma <i>et al.</i> , 2012 (33)	F, 22 y. o.	0 month	Apathy, bizarre behavior	Clinical evaluation		Improvement
10. Lopez-Sublet <i>et al.</i> , 2012 (34)	F, 27 y. o.	1 year	Personality changes, irritability, depression	Clinical evaluation		Improvement
11. Mishra <i>et al.</i> , 2014 (35)	M, 15 y. o.	6 months	Depressed mood, anxiety, passive suicidal ideation	Clinical evaluation	Antidepressants (Sertraline 25mg)	Improvement
13. Markakis <i>et al.</i> , 2014 (37)	F, 48 y. o.	0 month	Agitation	Clinical evaluation		Improvement
14. Farooqi <i>et al.</i> , 2014 (38)	F, 23 y. o.	0 month	Anxiety	Clinical evaluation		Improvement
16. Widman <i>et al.</i> , 2015 (40)	M, 18 y. o.	2 years	Mood lability, disinhibition, aggressivity	Psychiatric evaluation	Atypical Antipsychotics (Risperidone); care in psychiatri ward	Improvement
17. Witt <i>et al.</i> , 2015 (45)	M, 35 y. o.	6 months	Mild depression, significant emotional instability, bewilderment	Psychiatric evaluation; Beck Depression Inventory score: 13/63, N<10)	Antidepressants	Improvement (Beck Depression Inventory score: 6/63), vocational reintegration
18. Fauser <i>et al.</i> , 2015 (41)	F, 38 y. o.	6 years	Anxiety, emotional lability, moderate depressive symptoms	Clinical evaluation		No improvement
19. Sharma <i>et al.</i> , 2016 (43)	F, 30 y. o.	0 month	Apathy, behavioral changes	Clinical evaluation	Antidepressants	Improvement
21. Bougea <i>et al.</i> , 2017 (44)	F, 37 y. o.	0 month	Behavioral disorder	Clinical evaluation		Improvement

Table 4. Psychiatric symptoms associated to anti-GAD encephalitis

Sex: F: Female; M: Male. Y.o.: Years old.