ANTI GLUTAMATE-DECARBOXYLASE ANTIBODIES: A LIAISON BETWEEN LOCALISATION RELATED EPILEPSY, STIFF-PERSON SYNDROME AND TYPE-1 DIABETES MELLITUS

Anna SZŰCS[1], Gábor BARCS[1], Gábor WINKLER[2], Zsuzsanna SOÓS[2], András FOLYOVICH[2], Anna KELEMEN[1], Péter VÁRALLYAY[1], Anita KAMONDI[1]
[1]National Institute of Neuroscience, Budapest
[2]Szent János Hospital, Budapest

ANTI-GLUTAMÁT-DEKARBOXILÁZ ANTITESTEK: KAPCSOLAT A LOKALIZÁCIÓFÜGGŐ EPILEPSZIA, A STIFF-PERSON-SZINDRÓMA ÉS AZ 1-ES TÍPUSÚ DIABETES MELLITUS KÖZÖTT
Szűcs A, MD; Barcs G, MD; Winkler G, MD; Soós Zs, MD; Folyovich A, MD; Kelemen A, MD; Várallyay P, MD; Kamondi A, MD
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We present two patients with partial epilepsy, type-1 diabetes and stiff person syndrome associated with high serum auto-antibody levels to glutamate-decarboxylase (anti-GAD). Both patients were or have suffered from additional autoimmune conditions.
The presence of stiff person syndrome and elevated anti-GAD levels have to make clinicians look for additional autoimmune conditions including type-1 diabetes. On the other hand, the co-morbidity of partial epilepsy with autoimmune conditions in patients with elevated serum anti-GAD suggests an autoimmune mechanism of partial epilepsy in these cases.

Keywords: *stiff person's, anti-GAD, autoimmune epilepsy*

Két stiff-person-szindrómás, a szérumban emelkedett glutamát-dekarboxiláz-antitest (anti-GAD) -szintet hordozó beteg esetét ismertetjük. Mindketten parciális epilepsziában és 1-es típusú diabetes mellitusban, valamint további autoimmun betegségekben is szenvedtek.
Saját eseteink és az irodalom alapján arra következtetünk, hogy emelkedett szérum-anti-GAD-szinttel járó stiff-person-szindróma esetén további autoimmun betegségek, elsősorban 1-es típusú diabetes keresése indokolt. Másfelől, a parciális epilepszia társulása egyes, emelkedett anti-GAD-szinttel járó kórképekkel arra utal, hogy az ilyen esetekben anti-GAD-függő autoimmun patomechanizmus állhat az epilepszia hátterében is.

Kulcsszavak: *stiff person, anti-GAD, autoimmun epilepszia*

Correspondent: Anna SZŰCS MD, National Institute of Neuroscience;
H-1145 Budapest, Amerikai út 57. E-mail: szucsan@gmail.com

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Glutamate-decarboxylase (GAD) located within the nerve terminals of GABAergic neurons and the beta-cells of the pancreas, is the rate-limiting enzyme converting glutamate to gamma-hydroxy-butyrate (GABA). Auto-antibodies to GAD (anti-GAD) target the intracellular GAD presented to autoimmune reaction by B lymphocytes and HLA class II molecules[1]. Serum anti-GAD is detected in 80% of diabetes mellitus type-1 (DM1) patients[2, 3] as well as in late onset isolated cerebellar ataxia; autoimmune poly-endocrine syndrome, cerebellar ataxia with poly-endocrine autoimmunity; rheumatoid arthritis, myasthenia gravis, autoimmune thyreoiditis; and certain para-neoplastic syndromes[4].

Significantly higher anti-GAD (IgG) levels with different epitope specificity than in DM1 are present in 60-80% of patients with stiff person's syndrome (SPS); a rare condition (prevalence 1/1 000 000) characterized by stiffness and cramps of striated muscles, disturbing normal movement[5, 6].

The classical criteria of SPS are as follows[7]:
– Stiffness, tightness in trunk and proximal limbs,
– Prominent lumbar lordosis,
– Muscle cramps,

– Parallel muscle activity of antagonistic muscles simultaneously; in at least one axial muscle (the EMG may be normal),
– No brainstem-, basal ganglia-, or moto-neuron signs; normal sensory, autonomic and cognitive functions,
– Female preponderance,
– Association with other autoimmune diseases,
– Pulmonary/breast cancer in 15%.

Besides anti-GAD, additional auto-antibodies are found in SPS[8]: tyrogastric antibodies, islet-cell antibodies, auto antibodies against GABA-ergic neurons, 125/130 kd protein, amphiphysin and gephyrin, GABA A receptor-associated protein.

Ten percent of SPS patients have epilepsy and anti-GAD (IgG) was detected in seven out of 51 (13%) pharmaco-resistant partial epilepsy patients against none of 49 with generalized epilepsy[9].

We present two female patients sharing SPS, partial epilepsy and DM1; both suffering also in additional autoimmune conditions. We want to call attention to this multi-organ co-morbidity and to raise the possibility of anti-GAD related autoimmune aetiology in some epilepsies.

Case studies

PATIENT 1

A 51-year-old female had brain concussion at age 19. At age 29 complex partial and generalized tonic-clonic seizures started with right temporal interictal spikes seen on her EEG. Subcortical white matter lesions were detected on the MRI brain-scan of the patient; no hippocampal sclerosis was seen. No seizure freedom could be reached by adequately selected and therapeutic dose antiepileptic drugs.

At age 39 DM1 was diagnosed. At age 45 sacro-ileitis was diagnosed and sero-negative spondylarthritis was suspected.

At age 46, stiffness in the lumbar spine and limb muscles as well as painful cramps in the thigh developed. Electromyography at age 49 showed simultaneous motor activity in the antagonist muscles of the thigh, which could be suspended by intravenous diazepam. The diagnosis of SPS was supported by high anti-GAD titre in her serum [103.24 U/ml (reference <20)]. After unsuccessful treatment with Pregabaline and improvement on Diazepam; five sessions of plasma aphaeresis were instituted resulting in significant improvement of her stiffness. One month later she has become seizure free for six months on unchanged antiepileptic medication.

PATIENT 2

A 69-year-old female had partial epilepsy from age 20, treated with phenytoin and carbamazepine. She had generalized tonic-clonic seizures and left temporal lobe spikes on her EEG. After antiepileptic treatment lasting for 15 years, she has become seizure-free, so the antiepileptic medications could be discontinued. Her DM-1 started at age 40.

At age 58 stiff lower limbs and trunk developed with hyper-lordotic posture and painful cramps in leg-muscles. She was unable to bend and had opistotonus when lying on her back. Minimal effort caused tachycardia. The whole-spine MRI scan was normal, the MRI brain-scan revealed cerebellar atrophy. Electromyography (without parallel agonist-antagonist muscle testing) was normal, but there was typical clinical presentation for SPS: the small lady could be pushed into the MRI-tube supported at her low back only; not bending at all. Her serum anti-GAD (IgG) was 5100U/ml (reference<20) supporting the diagnosis of SPS. Treatment with clonazepam and baclofen decreased her muscle-stiffness, she was unable to walk without them. Intravenous administration of Methylprednisolon 1000 mg/day for a week did not help. Her mobility worsened over the years, her cerebellar ataxia also progressed till she became wheelchair-bound.

Because of her diarrhoea and weight loss, bowel biopsy has been carried out; and positive anti-gliadin antibodies were found in her serum, celiac disease was diagnosed at age 64.

Discussion

The diagnosis of SPS was supported by the clinical presentation and high serum anti-GAD antibody titres in both patients; no CSF testing was performed. EMG evidence was present only in patient 1. The autoimmune mechanism of both SPS and epilepsy of patient 1 is supported by her improvement of muscle stiffness as well as becoming seizure free; in response to plasma exchange therapy. The steroid treatment of patient 2 proved to be insufficient.

The apparently distant combination of SPS, DM1 and partial epilepsy was described by *Solimena* and colleagues back in 1988[10] and was reported later[11]. Although we haven't performed full autoimmune screening in our patients, their laboratory check-up based on their specific syndrome revealed additional autoimmune conditions e.g. sacro-ileitis (Patient 1); celiac disease and progressive cerebellar ataxia (Patient 2).

Celiac disease shares the demographic features of SPS. Serum antigliadin antibodies (diagnostic for celiac disease) are found in 30-40% of sporadic cerebellar ataxia patients[12]. Because celiac disease may manifest as "gluten ataxia" and cause seizures[13]; the epilepsy and cerebellar ataxia of patient 2 could be related both to her celiac disease and her high serum anti-GAD level.

Both SPS and epileptic seizures respond to GABAergic agonists as benzodiazepines, sodium valproate, baclofen and vigabatrin. There are decreased cortical GABA levels in both conditions[14–16] as evidenced by MR spectroscopy, suggesting an aetiological role of low GABA-related cortical inhibition[17–19].

It has been recently shown that GAD-67 is expressed in hippocampal mossy fibers of temporal lobe epilepsy patients[20] offering a clue why partial epilepsy unlike generalized epilepsy is associated to GAD autoimmunity; and intrathecal anti-GAD synthesis has been found in 77% of pharmaco-resistant temporal lobe epilepsy patients with elevated serum anti-GAD[11]. Low cortical GABA may be due to decreased glutamate-GABA conversion; as a result of anti-GAD autoimmunity. The beneficial effect of corticosteroids, intravenous immunoglobulin and plasma-aphaeresis in SPS support this hypothesis, and the role of autoimmunity in epilepsy is supported by the intra-thecal presence of anti-GAD antibodies found in status epilepticus patients[21].

The combination of different autoimmune conditions in our patients suggests that the diagnosis of SPS and high anti-GAD level in the serum have to make clinicians seek for co-morbid autoimmune conditions and keep in mind the risk (up to 10%) of the co-occurrence of epilepsy in these patients.

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