Neurological syndromes associated with GAD antibodies

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Overview
- Stiff person syndrome (SPS)
- Cerebellar ataxia
- Other neurological syndromes associated with GAD antibodies
- Case presentation
- Role of GAD antibodies in SPS and cerebellar ataxia

Glutamic acid decarboxylase (GAD)
- Rate-limiting enzyme for the synthesis of γ-aminobutyric acid (GABA)
- Two isoforms exist which are encoded in different genes:
  - GAD65: CNS and pancreas (β cells)
  - GAD67: CNS
- Antibodies against GAD found in type 1 diabetes mellitus (DM1) patients (65-80 %)

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GAD antibodies

- Much higher titers of antibodies against GAD are also found in SPS, cerebellar ataxia and treatment refractory epilepsy
- A. Saiz et al (Brain; 2008; 131) found intrathecal synthesis (IS) of GAD antibodies in:
  - 85% of SPS subjects
  - 100% of subjects affected by sporadic late-onset cerebellar ataxia
  - 86% of subjects affected by other neurological syndromes (epilepsy, limbic encephalitis and paraneoplastic neurological syndromes)

Stiff person (man) syndrome

- Sporadic and rare disorder, described initially by Moersch and Wolman in 1956 (Mayo Clinic)
- The association with GAD antibodies described in 1988
- Despite its older name, SPS is in fact more common among women
- Estimated prevalence 1 per 1 million

Stiff person syndrome

- Clinical presentation:
  - Gradual onset stiffness and superimposed episodic spasms
  - Rigidity is typically absent during sleep
  - Episodic spasms precipitate by unexpected noises, tactile stimuli, or emotional upset
  - Anxiety and task-specific phobias are frequent, fear of falling, can lead to erroneous diagnosis of a psychiatric disorder
  - SPS is frequently associated with autoimmune endocrine diseases (35-60% have diabetes)
  - Strong association with the DRβ1 locus (0301 and 0101 alleles) and DQβ1 locus (0201, 0203 and 0005 alleles)
Stiffness and rigidity causes hyperlordosis and difficulty bending or turning
Gait becomes slow, deliberate and wide (board-like posture)

SPS variants
- Stiff limb syndrome: affects a leg usually, most patients develop generalized SPS
- SPS-plus:
  - Concomitant ataxia seen in 10%: SPS-cerebellar variant
  - Epilepsy occurs in 5-10%
  - Rare to see cognitive decline
  - Progressive encephalomyelitis with rigidity and myoclonus (PERM)

Progressive encephalomyelitis with rigidity and myoclonus (PERM)
- Severe syndrome of subacute onset, relentless and rapid progression, poor prognosis in most cases
- Hyperekplexia (startle), autonomic dysfunction, ataxia, brain stem and long tract signs
- Associated with antibodies against GAD and GlyR
- A PERM case with antibodies against GlyR and NMDAR has been described (M. Turner et al.; Neurology; 2011; 77)
- cMRI of the brain usually normal
- Neuropathology: in general widespread perivascular cuffing and loss of interneurons in the brainstem and spinal cord
SPS and autoantibodies

- More than 85% have antibodies against GAD (elevated at least 50 times above baseline)
- Antibodies against GABARAP (GABA receptor associated protein) have been found in 70% of GAD positive sera
- SPS is a paraneoplastic syndrome in up to 5% of cases, mostly breast cancer
  - Antibodies against amphiphysin
  - Antibodies against gephyrin found in one subject affected by mediastinal cancer


Stiff person syndrome


Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin

*Spinal cord section from rat exposed to IgG against amphiphysin showing infiltration around blood vessels*
Diagnosis of SPS

- Requires high index of suspicion

**Criteria**
- Muscle rigidity in the limbs and axial muscles, prominent in the abdominal and thoracolumbar paraspinals
- Continuous concurrent contraction of agonist and antagonist muscles (clinically and by means of electromyography)
- Episodic spasms precipitated by unexpected noises, tactile stimuli, or emotional upset
- Presence of GAD antibodies
- EMG: continuous low-frequency motor unit firing at rest in agonist and antagonist muscles
- cMRI of the brain and spinal cord is normal

Treatment of SPS

- Drugs that improve cortical and spinal inhibition:
  - BZ: These drugs are GABA-A agonists. Diazepam is the first option, required dose 60-120 mg/d. Other BZ: clonazepam, alprazolam, lorazepam (4-8 mg/d)
  - AED: most effective vigabatrin, gabapentin and levetiracetam
  - Antispasticity drugs: Baclofen (GABA-B agonist)
  - Tizanidine: α 2 adrenergic receptor agonist
  - Dantrolene: locally acting muscle relaxant

- Immunomodulation:
  - Corticosteroids: usually disappointing
  - IVIG: preferred treatment option. 2g/kg tested in a controlled trial. Up to 30% do not respond to IVIG, benefit lasts 1-4 mo.
  - Plasmapheresis: beneficial in up to 40% of patients
  - Rituximab: B-cell depleting monoclonal antibody

M. Dalakas: Current Neurology and Neuroscience Reports; 2008; 8.

SPS and treatment

← Before and after treatment with IVIG, M. Dalakas et al; NEJM; 2001; 345
Cerebellar ataxia with GAD antibodies

- Idiopathic and rare disease of unknown prevalence
- Affects middle-aged women mostly, more common in DM1 individuals (around 50%)
- Associated polyendocrine autoimmunity
- Varying degree of cerebellar atrophy has been found in some cases
- Usually treatment refractory
- Some cases are a paraneoplastic syndrome

A. Saiz (Brain; 2008; 131)
- In one case series 7 individuals had a subacute onset (weeks < 6 mo) and 10 displayed a chronic course (1-6 y)
- Intrathecal synthesis of GAD antibodies found in all affected

Both C: Selective loss of Purkinje cells. D. Loss of pancreatic islets

(Aihara, K et al. J Neural Neurosurg Psychiatry, 2008)
**LETTERS**

Cerebellar astrocytes associated with neurenteric thymic carcinoma and GAD antibodies

Gliallike cells may act as a reservoir for some of the neurenteric axis in the cerebellum. They are assumed to be involved in the development of these structures, which are consistent with both malformations and tumors that develop in the cerebellum. This article focuses on the association between neurenteric thymic carcinoma and GAD antibodies, which may indicate the presence of these structures in the cerebellum. The paper discusses the potential role of these cells in the development of neurenteric thymic carcinoma and the significance of GAD antibodies in the pathogenesis of this disease.

**Figure A**: Section of rat cerebellum incubated with the serum of the patient (1:250) and developed with indirect immunofluorescence. The pattern of reactivity corresponds to the characteristic distribution of glutamic acid decarboxylase (GAD) in nerve terminals of the cerebellum (m, molecular layer; p, Purkinje cell layer; g, granular cell layer). (B) Section of the tumour of the patient incubated with monoclonal GAD antibody. Tumoral cell expression of GAD is detected. (C) Contiguous section of the tumour immunostained with a monoclonal antibody against CD20, showing infiltrates of B lymphocytes.


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**Table 1**

Clinical and Immunological Findings of Patients with Cerebellar Astrocytes and SPS

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>GAD positive</th>
<th>SPS + GAD positive</th>
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<tbody>
<tr>
<td>Age (mean, range)</td>
<td>54 (25–70)</td>
<td>56 (30–75)</td>
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<tr>
<td>Gender</td>
<td>M: F = 26:24</td>
<td>M: F = 24:25</td>
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<td>Other relevant clinical features</td>
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<td></td>
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<tr>
<td>Common ataxia</td>
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<td>22/25</td>
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<tr>
<td>Late-onset cerebellar ataxia</td>
<td>18/16</td>
<td>17/18</td>
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<td>Other neurological syndromes</td>
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**Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic dyes for this association**

Alvaro Bataller1, Nieves Blanco2, Lidia Sabater1, Félix Géminiani1, Luis Remeli1, Ruarte Carrión3, Luis Ramírez-Serrano2, and Francisco Giral3

n = 50 subjects
- 22 "stiff person’s syndrome" (SPS)
- 17 late-onset cerebellar ataxia
- 11 subjects affected by other neurological syndromes:
  - 4 epilepsy (EP)
  - 2 limbic encephalitis (LE)
  - 1 myasthenia gravis (MG)
  - 4 paraneoplastic neurological syndrome (PNS):
    - 2 PCD (non-SCLC, thymic carcinoma)
    - 1 paraneoplastic LE (SCLC)
    - 1 paraneoplastic encephalomyelitis (Pancreas)
Other neurological syndromes associated with GAD antibodies

- Juvenile ceroid lipofuscinosis (Batten’s disease) ⇒ High titers (D. Pearce et al 2004).
- 3 subjects affected by EPS (H. Meinck et al 2001) and 1 affected by a paraneoplastic movement disorder (G. Verme, 2011).
- Found in some individuals affected by tardive dyskinesia (A. Yarlagadda et al 2011).

Case presentation

- 56 y.o. from the Philippines
- Lacks FH of neurodegenerative diseases
- Seven-eight years ago she developed a stiff leg with gait difficulties first
- Later she developed involuntary movements of the left arm
- Initial w/u with MRI and lp
- OCB were found, neuroinflammation suspected.

- A couple of years later she developed a ketoacidosis while she was in the Philippines
- GAD-abs were found in her serum, SPS considered a possible diagnosis
- 2009 came to our center.
  - At the time strictly left symptoms with involuntary movements and hemiataxia. The muscular tone was increased in the left arm and leg
  - Extensor plantar sign in the left was found
  - She had frontal release signs (crying)
- A new lp show OCB and an intrathecal production of GAD abs
- DAT-scan: mild reduction in the uptake left putamen
Mild cerebellar atrophy

Mild frontal atrophy

Marked atrophy of the left cerebellar hemisphere and the vermis
Ig G (serum) 1120 mg/dl (700-1600)
• Albumin (serum) 4390 mg/dl (3500-5300)
• IgG (CSF) 2.89 mg/dl (<3.4)
• Albumin (CSF) 20.70 mg/dl (<35)
• GAD Ig G ab index 6.49 (<2.0)
• GAD ab (serum) 596860 U/L (ref <70)
• GAD ab (CSF) 9682 U/L (ref <70)
• Lacks antibodies against Gly-R and NMDAR

Paraneoplastic antibodies and CT scans of her chest and abdomen were normal
• Lacks mutations for HD, DRPLA, SCA 1, 2, 3, 6 and 7
• CSF tau = 439 (ref < 400 ng/L), P-tau = 90 (ref < 60 ng/L) and NFL = 920 (ref <600)
• We have tried steroids and IVIG without benefit
• Februari 2011 major deterioration, started to fall, send to a nursing home. Broke her hip
• Confined to a wheel chair, can't stand anymore and has developed generalized ataxia
• She is fatigued and has significant speech problems. Recurrent vomiting. Normal gastroscopy
August 2011: Plasmapheresis and IVIg given for 5 months had a mild benefit but the ataxia is unchanged.

In November last year the subject declined the continuation of plasmapheresis.

January 2012: Her condition worsened and pronounced behavioural disturbances appeared. Agitated and started to scream for no obvious reason.

Requires personal assistants. She has developed paranoia. Acts in a childish (echolalia).

March 2012 Rituximab was given without improvement.

**Dx:** Encephalomyelitis with cerebellar ataxia associated with GAD antibodies.

Screening for tumours in paraneoplastic syndromes: report of an EFNS Task Force

- Tumour screening depends on the nature of the antibody and the PNS.
- Depends also on gender and age.
- Regular examinations every 3-6 mo up to 4 years.
What is the role of GAD antibodies?

- Scarce neuropathological abnormalities found in SPS
- Reduced GABA levels found in the brain in SPS case by means of MRS and PET
- Treatment responses in SPS support a functional role of GAD antibodies
- How do these antibodies cross the BBB and how are they uptake?
- What is the role of T-cells?
- Some evidence of a possible functional role has emerged
- Epitope specificity seems to explain the clinical presentation (Manto, U et al 2011)
- GAD antibodies are considered biomarkers of autoimmunity

Thanks!