• Easy To Diagnose And Treat, If You Think Of It •

Stiff Person Syndrome

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INTRODUCTION

Stiff person syndrome (SPS) is characterised by progressive rigidity and spasms affecting axial and limb muscles. Most patients with SPS have antibodies against the *glutamic acid decarboxylase-65* (GAD65), *Amphiphysin*, *GABARAP* or *Gephyrin*, limiting production of neurotransmitter *gamma-aminobutyric acid* (GABA).

CASE REPORT

A 39-year-old woman started complaining about episodic and painful muscles contractions, initially limited to the inferior right limb, with increasing frequency and intensity, which progressed over time. She had neuroimaging examinations (CT and MRI scans) that revealed **triventricular hydrocephalus** with aqueductal stenosis. Two years later, after neurosurgical assessment, she underwent endoscopic third ventriculocisternostomy, with only little and temporary improvement after the procedure (**Figure 1**). Seven years after symptoms onset, due to progressive worsening of clinical signs and symptoms, she was admitted to our **Neurological Unit of Careggi Hospital of Florence**. On admission, gait was bizarre, slow and wide-based. She presented paroxysmal episodes of muscles **tightness** especially on right inferior limb, but extended at the contralateral inferior limb, dorsal and mastication muscles. These **spasms** could be present at rest, but also triggered by emotional upset, tactile stimuli, sudden movements and were variable in intensity, distribution and duration, lasting usually few seconds. She presented hypertrophy of dorsal muscles, with lumbar hyperlordosis. Frank hyper-reflexia was seen in all four limbs, without plantar extension. She did not exhibit any other neurological abnormalities, on exception of mild reactive **depression and anxiety** disorder. MRI brain scan was negative for new lesions. It was impossible to perform cerebrospinal fluid tap test because of the patient's inability to muscles relaxation and hypersensitive reactivity to stimuli (**tactile startle response**). Electromyography showed constant firing of examined motor units, even at rest, with persistent tonic contraction of voluntary muscles (**Figure 2, 3**). Blood examinations excluded diabetes, anemia, celiac and neoplastic diseases. She presented abnormal title of antinuclear antibodies (ANA) (1:320), serological features of Hashimoto-like **thyroiditis** with hypothyroidism and high titre of **anti-GAD antibodies** (>5000 IU/mL, n.v.<5). **Benzodiazepine** three times per day obtained symptomatic relief of muscles stiffness, confirming the suspect of SPS. Then was administered a single treatment of anti-CD20 monoclonal antibody, **Rituximab**, at 375 g/m^2 as suggested in letterature. Six month evaluation revealed optimal response to immunotherapy, with lasting clinical remission.

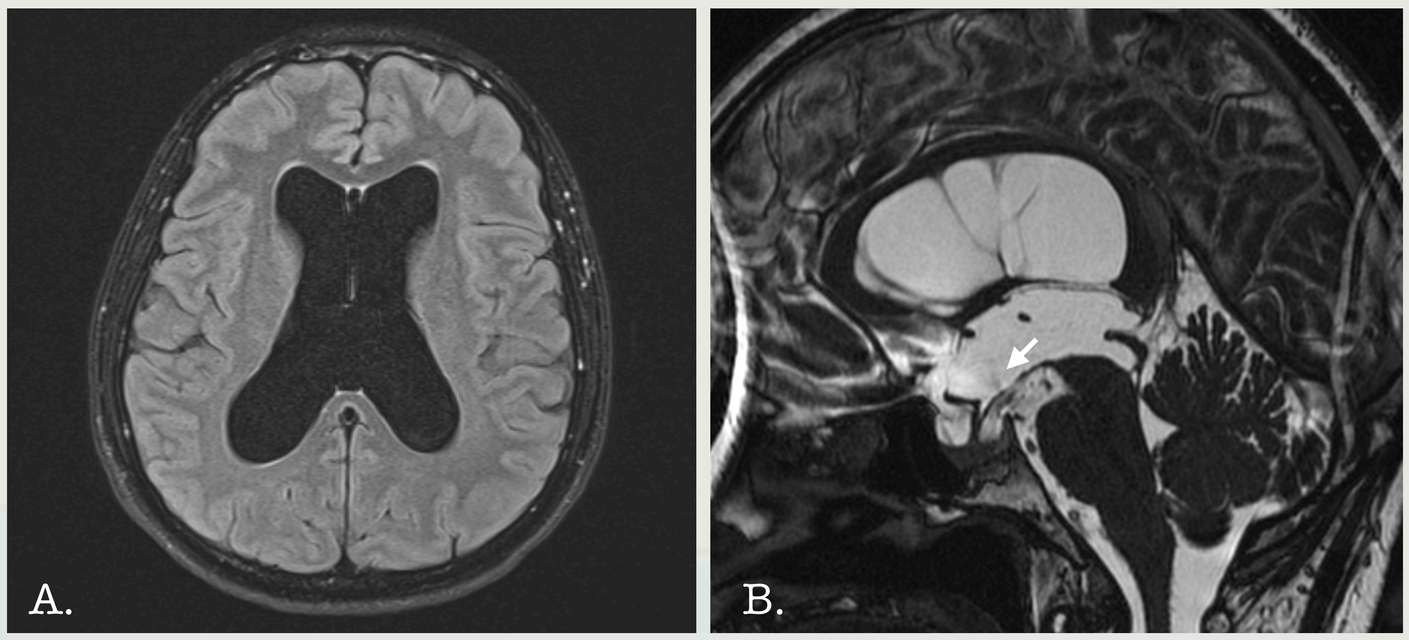

FIGURE 1: MRI T2 FLAIR-weighted sequence showing massive dilatation of the ventricles in acqueductal stenosis (**A**). After ventriculocisternostomy, MRI T2 CISS sequences images revealed CSF flow (*flow void*, see **arrow**) through the floor of the third ventricle between the tuber cinereum and the mammillary bodies, connecting ventricular system with prepontine cistern (**B**).

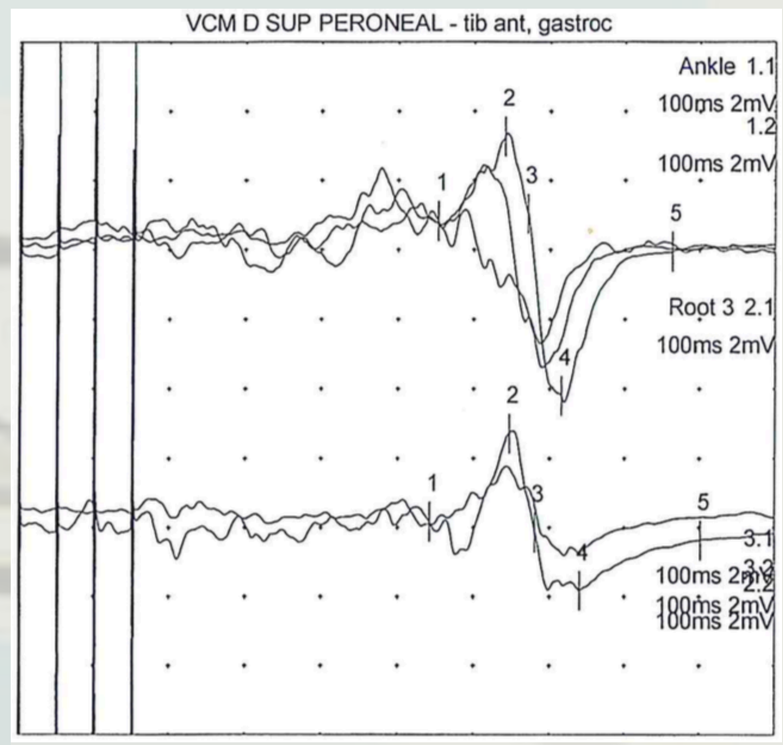

Figure 2: Increased reflex excitability in SPS patients. Stimulation of right superficial peroneal nerve (4 pulses 40 Hz) elicits large and synchronous late response on extensor muscle (tibialis anterior) and flexor (soleus). Needle registration confirmed continuous motor unit activity in agonist and antagonist muscles, despite attempted relaxation.

Symptomatic therapy	Usual doses*	Level of evidence†
Sedatives and antispasticity drugs		
Diazepam	5–100 mg/day	C
Clonazepam	2.5–6 mg/day	C
Alprazolam	2–4 mg/day	C
Tizanidine	6–36 mg/day	C
Baclofen—oral	10–60 mg/day	C
Baclofen—intrathecal	50–150 μg/day	C
Propofol	15–30 μg/kg (boluses), 10 μg/kg min (maintenance)	C
Dantrolene	50 mg four times a day	C
Botulinum toxin	Variable	C
Antiepileptic drugs		
Levetiracetam	500–1000 mg twice a day	B
Pregabaline	75–150 mg twice a day	C
Gabapentine	300–900 mg three times day	C
Tiagabine	4–8 mg once or twice a day	C
Valproate	300–600 mg twice daily	C
Vigabatrin	500–1500 mg twice daily	C
Non-useful (U) or harmful (H)		
Milacemide (U)	800–2400 mg/day	C
Reserpine (H)	0.5 mg intravenous	C
Clomipramine (H)	20 mg intravenous	C
Immunotherapy		
Intravenous immunoglobulin	2 g/kg in 2–5 days	B
Rituximab	375 mg/m^2	B
Plasma exchange (PE)	5 PE in 1–2 weeks	C
Corticosteroids (prednisone)	50–60 mg/day	C
Mycophenolate mofetil	2 g/day	C
Tacrolimus	3 mg/day	C
Cyclophosphamide	1–5 mg/kg/day	C
Azathioprine	1–2.5 mg/kg/day	C
Methotrexate	15–20 mg/day	C

Table 1: Therapeutic options in patients with Stiff Person Syndrome.

Nervo / Posizioni	Latenza ms	Amp.2-4 mV	Amp.2-4 %	TTMC ms
D COMM PERONEAL - Tib Ant				
Caput Fibulae	3,45	15,5	100	
Paraspinale	14,45			
Cranio	26,65	21,1	136	12,20
S COMM PERONEAL - Tib Ant				
Caput Fibulae	3,40	16,2	100	
Paraspinale	14,55			
Cranio	26,95	14,6	90,4	12,40
D ULNAR - ADM				
Polso	2,25	17,8	100	
Cranio	19,05	9,1	51,2	

Figure 3: Motor evoked potentials (MEPs) revealed normal central motor conduction times, with reduced excitability thresholds and increased intensity of MEP stimuli in resting right leg muscles.

CONCLUSIONS

SPS is a rare autoimmune disorder, with progressive and fluctuating muscles rigidity and superimposed spasms triggered by heightened sensitivity to external and internal stimuli. It is important to recognise clinical signs and symptoms of SPS, as treatment may be effective in reducing its related disability. GABA-enhancing drugs are largely used in order to obtain pharmacologic control of symptoms. Immunotherapy, instead, is aimed at modulation of the immune process. On literature, intravenous immunoglobulin and Rituximab obtained the highest Level of Evidence (**Table 1**).

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