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Case report

# Progressive encephalomyelitis with rigidity presenting as a stiff-person syndrome

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**Abstract**

Diagnosis criteria of stiff-person syndrome (SPS) include progressive, fluctuating muscular rigidity and spasms with normal neurological examination. The presence of unusual features such as prominent limb rigidity with segmental signs and contracture, evidence of brainstem dysfunction, profound autonomic disturbances, CSF pleiocytosis or MRI abnormalities in patients with SPS presentation allows to classify these patients as progressive encephalomyelitis with rigidity (PER). We report a 50 year-old woman suffering from severe painful spasms of abdominal wall and limb muscles. Neurological examination showed pyramidal signs. EMG disclosed continuous muscle activity with superimposed discharges. Treatment with high doses of diazepam and baclofen led to moderate improvement of generalised stiffness. However, the right arm became more rigid with oedema and vasomotor changes. Subsequently, bilateral nystagmus and internuclear opthalmplegia appeared. There was mild CSF pleiocytosis. Associated auto-immune thyroiditis was found with positive anti-microsome antibodies and decreased thyroid hormones. Search for profound neoplasm was negative. The patient had three subacute bouts then she improved with methylprednisolone.

The initial clinical presentation mimicking a SPS with subsequent diffuse involvement of the central nervous system and a striking localisation of a severe rigidity to one arm allowed to suspect the diagnosis of PER. The relationship between SPS and PER remains unclear because of the rarity of these disorders. The observation reported in this paper gives evidence that both the disorders are probably two clinical presentations of the same pathogenic process. © 2002 Published by Elsevier Science Ltd.

*Keywords*: Progressive encephalomyelitis; Segmental rigidity; Stiff-person syndrome; Thyroiditis; Corticosteroids

## 1. Introduction

Stiff-person syndrome (SPS) first described by Moersch and Woltman [1] is a rare acquired disorder of adult life characterised by progressive and fluctuating muscle rigidity and spasms. In 60% of cases, it is associated to antibodies against glutamic acid decarboxylase (GAD) and can sometimes be paraneoplastic [2]. In some patients with SPS presentation, atypical clinical signs (such as prominent limb rigidity with segmental signs and contracture, evidence of brainstem dysfunction, profound autonomic disturbances, CSF pleiocytosis and MRI abnormalities) were reported suggesting progressive encephalomyelitis with rigidity (PER) [3,4]. Because of the rarity of the two disorders the relationship between SPS and PER remains unclear. We report the history of a patient with PER and discuss the link of this entity to SPS.

## 2. Case report

A 50 year-old woman had hypertension and dyslipidemia for three years. On April 21, 1996, she suddenly developed painful spasms and rigidity of the abdominal wall muscles. Spasms extended to the lower limbs within three days. On examination, five days after onset, there was a generalised stiffness sparing the face, and superimposed contractures aggravated by voluntary movements and external stimuli such as noise or touch. The patient was unable to walk unaided and to bend her neck forward; she could not move her legs at the hip, knee and ankle joints because of the muscle stiffness. The abdominal wall was hard as if with peritonitis. No hyperlordosis was observed. Rigidity and spasms disappeared during sleep. Initial neurological

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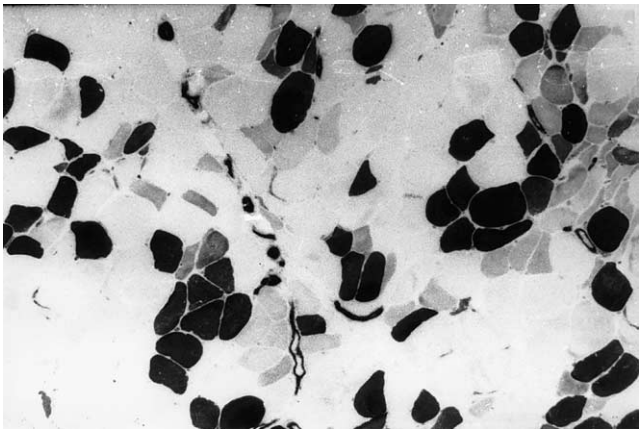

Fig. 1. Muscle biopsy showing neurogenic atrophy with type grouping and predominance of type II fibres.

examination was otherwise normal. Fifteen days after onset, examination showed brisk tendon reflexes, positive bilateral Babinski and Rossolimo signs. Routine blood tests (including: glucose, Na, K, Ca, Cl, haemoglobin, tests for liver and kidney functions, sedimentation rate, protein electrophoresis, treponemal agglutination test) were normal. There was a slight increase in WBC count (13.400 $mm^{-3}$) and serum creatine kinase level (665 UI/ml). CSF contained 10 WBC/ml and 0.28 g/l proteins.

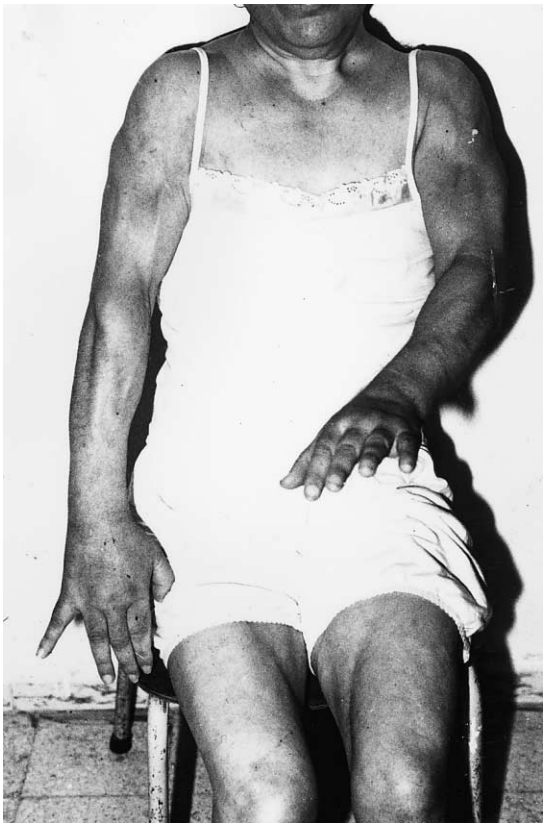

Fig. 2. The patient is asked to raise both arms to horizontal position. Elevation is limited for left arm and impossible for right arm, which remains sticked to the chest. Note the rigid abnormal posturing of the right fingers.

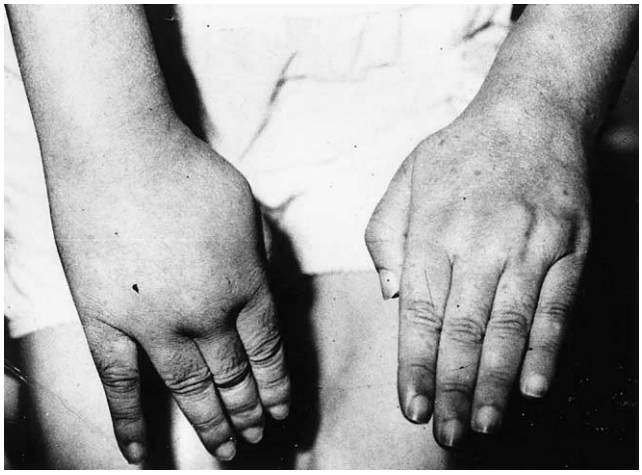

Fig. 3. Oedema of the right hand. Compare to the left hand.

Electromyography (EMG) of limb and paravertebral muscles showed neurogenic changes and abnormal muscular activity at rest with paroxystic discharges. Motor and sensory nerve conduction velocities were normal. Muscle biopsy showed neurogenic atrophy with type II fibre predominance (Fig. 1) and semi-thin nerve sections of sural nerve biopsy showed normal density of myelinated fibres. Electroencephalography was normal. Visual evoked potentials (EP) were normal. Sensory EP showed reduced amplitude of spinal somatosensory potentials (SEP) after stimulation of the ulnar nerves. T2 weighted cerebral MRI showed small hypersignals of the subcortical white matter in the hemispheres. Breast examination, chest X-ray, abdominal and pelvic echograpy were normal. Gastric endoscopy showed peptic ulcer. Immunological testing found positive anti-thyroid antibodies (anti-thyroglobulin $> 1/80$; anti-microsomes $> 1/1600$) suggesting auto-immune thyroiditis. Hypothyroidism was confirmed by serum FT4 $< 0.2$ ng/dl and TSH $> 50$ μUI/ml. Other immunological tests (including rheumatoid factor, immunoelectrophoresis, complement, circulating immune complexes, anti-nuclear and anti-smooth muscle fibres antibodies) were normal. Test for anti-GAD auto-antibodies could not be performed.

A treatment with oral diazepam at a daily dose of 45 mg/day was given to the patient. It relieved the spasms, and to a lesser extent, the contracture of abdominal and limb muscles.

On March 1997, the patient complained of aggravation of the stiffness especially in her right upper limb leading to inability to move the arm. The patient's arm was sticked to her chest with pronation of the hand and a severe rigidity of the fingers (Fig. 2). The right hand was cyanotic and swollen (Fig. 3). X-ray of the right shoulder was normal. Diazepam was increased to 75 mg/day and associated to 80 mg/day baclofen and a partial relief of the stiffness was observed. On October 1997, a new attack occurred and examination showed horizontal bilateral nystagmus, anterior internuclear ophtalmoplegia and generalised

Table 1
Main characteristics of SPS and PER (CNS: central nervous system; CSF: cerebrospinal fluid; GAD: glutamic acid decarboxylase; MRI: magnetic resonance imaging)

| | SPS | PER |
|---|---|---|
| Stiffness | Predominantly axial | Limbs, axial |
| Stimulus sensitive painful spasms | Constant | Possible |
| Hyperlordosis | Constant | Absent |
| Onset | Insidious | Acute |
| Course | Protracted, tends to stabilise | Fluctuating, severe |
| CNS involvement | No | Yes |
| Pyramidal signs | No | Yes |
| Oculomotor involvement | No | Yes |
| CSF | Normal | Pleiocytosis |
| Positive Anti-GAD antibodies | Frequent | Possible |
| Association to auto-immune disease | Frequent | Possible |
| Muscle biopsy | Normal | Neurogenic changes |
| Cerebral and spinal MRI | Normal | May be abnormal |
| CNS pathology | Absent | Perivascular inflammation |

intermittent spontaneous myoclonus. The patient was given an intravenous course of 1 g/day methylprednisolone for 5 consecutive days. One week later, we observed a dramatic improvement with progressive decrease of the rigidity of the body and especially of the right upper limb. She continued to improve over six months of follow up and was able to walk with minimal aid, to dress herself and to dress her hair. Vasomotor signs of the right hand decreased. Muscle consistence was normal at rest and mildly increased at voluntary movements. The patient is now stabilised under 10 mg/day diazepam, 20 mg/day baclofen and substitutive treatment of hypothyroidism. Search for profound neoplasm two years and a half after onset is still negative.

## 3. Discussion

The clinical features of the patient reported here are characterised by acute onset of limb and axial rigidity and spasms without hyperlordosis. Three subacute bouts occurred with aggravation of rigidity and more diffuse involvement of central nervous system (pyramidal, vestibular, oculomotor signs). The bouts were followed by a spontaneous slow recovery. A dramatic improvement was obtained during the last attack of the disease with high doses of methylprednisolone. In this patient, two diagnosis can be discussed: SPS or PER.

In typical cases of SPS, onset is insidious with aching and tightness of axial muscles spreading to limb muscles, persistent contraction of the thoracolumbar and paraspinal and abdominal muscles leading to hyperlordosis and board like rigidity of the abdominal muscles [5]. Rigidity is associated to stimulus sensitive painful muscle spasms. No other neurological signs are observed, the disease progresses slowly with little fluctuations and tends to be stabilised under treatment [5]. EMG shows continuous motor unit activity with normal motor unit morphology and peripheral nerve conduction velocities. CSF and MRI are normal. Anti-GAD antibodies and association to auto-immune endocrine disease are helpful but not consistent [5]. In some patients, SPS is a paraneoplastic manifestation [6]. Pathological examination of the central nervous system in patients with SPS has been reported to be normal [5].

Some features (such as prominent limb rigidity with segmental signs and contracture, evidence of brainstem dysfunction, profound autonomic disturbances, CSF pleiocytosis and MRI abnormalities) can occur in patients suspected to have SPS. Such features are atypical for SPS, make this diagnosis questionable and lead to suspect the diagnosis of PER [5]. The latter is a progressive disorder characterised by painful spasms and rigidity, brainstem or long tract signs appearing within a year after onset, segmental limb rigidity [4] and a rapid course [7]. CSF is inflammatory with mild pleiocytosis [7] and T2 cerebral MRI sequences may show increased signal intensity throughout the spinal cord and the brainstem in some patients [8]. Response to diazepam seems milder in PER as compared to SPS [9,10]. Pathological findings are characterised by lymphocytic perivascular infiltrates and gliosis at brainstem and spinal cord [4,5,8].

The extent to which the clinical expression and the pathogenesis of SPS and PER may overlap is not clear. Main characteristics of the two disorders are summarised in Table 1. Only two patients with SPS features preceding the development of PER have been reported in the literature [5,11]. This is the case in our patient: the clinical picture at onset fitted with the diagnostic criteria for SPS; however, absence of hyperlordosis which is an almost universal sign in SPS and appearance of neurological abnormalities dealing with a diffuse involvement of the central nervous system ruled out this diagnosis. Meinck et al. considers two out of eight patients diagnosed as SPS to have probable PER because of accessory neurological symptoms [2].

Due to the identification of auto-antibodies against GABAergic neurones in both PER and SPS — but not in other neurological disorders — some authors suggest that

the two disorders are closely related [12], SPS possibly representing a benign oligosymptomatic manifestation of a spectrum of encephalomyelitis with auto-immunity against GABAergic neurones [2].

In SPS, continuous muscle activity was related to dysfunction in the descending inhibitory pathways controlling motor neurone excitability. In PER, due to the absence of extensive neurophysiological studies, the mechanism of segmental rigidity could be inferred from the similarities with the segmental rigidity observed in some cases of spinal tumour or spinal ischemia, syringomyelia, or paraneoplastic myelitis. In all these disorders, preferentially involving the grey matter of the spinal cord, continuous muscle activity was related to spinal interneuronitis [2,7,10]. The study of stiff people is of current interest. According to a recent study [14] based on clinical, biological, electrophysiological features and on the course of the disease in 23 stiff patients, the authors attempted to define three subgroups: stiff-trunk syndrome (stiff-man syndrome), stiff-limb syndrome and PER. Major distinctive feature of PER was an acute course leading to death within one year as opposed to SPS and stiff-limb syndrome which have chronic course. Our patient does not fit in any of the defined subgroups and is an example of the difficulty to classify the stiff persons. The association of PER and auto-immune thyroiditis, like in our patient, has been previously reported in one patient [13] but clinical presentation in this patient (bulbar involvement and normal muscle tone in limbs) was not confusing with SPS. A patient with PER has been reported to respond to high doses corticosteroids and this has been considered by the authors to be consistent with an inflammatory process in this disorder [8]. In our patient, both the association of an auto-immune disorder to PER and the improvement of the segmental rigidity under methylprednisolone argue for the hypothesis of an auto-immune mediated inflammation. It seems that SPS and PER are caused by auto-immunity against GABAergic neurones. The degree of the inflammation induced by this auto-immune reaction could account for the differences in the clinical and pathological expression between SPS and PER: limitation to the spinal interneurons could account for the stiffness, whereas spreading to the CNS could account for the presentation as an encephalomyelitis. The cause of the difference in the course of the disease in the two disorders (with stabilisation over time such as in SPS and a severe course such as in PER) remains unclear. We can speculate that it could be related to some genetic background.

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