the muscles become spasmodic, starting with the head and neck in the form of trismus and risus sardonicus, eventually spreading to every muscle in the body, with nearly continuous convulsions getting worse with the slightest stimulus. The convulsions progress, increasing in intensity and frequency until the backbone arches continually. Convulsions are followed by postictal depression. Death comes from asphyxia or by exhaustion from the convulsions. The subject dies within 2–3 h of exposure.

Chronic tetanus
The symptoms observed in the acute form, such as painful spasmodic contraction of the voluntary muscles, usually involving the jaw, face and neck, less frequently those of the trunk, the extensors of the spine and limbs, will in time be seen in the chronic form, with the exception that a paroxysm is followed by an interval of varying duration when there is relaxation of the muscles and freedom from pain. During this interval, the patient is enabled to take nourishment and stimulants thus preventing the exhaustion seen in the acute attacks. When recovery takes place, which occurs far more frequently than in the acute form, the spasms occur at longer intervals and in a lighter form till they cease entirely. Relapses may occur, sometimes unexpectedly, and may terminate fatally. Our patient did not remember any injury with rusted steel.

Neuromyotonia (Isaac’s syndrome)
This rare neuromuscular disorder is caused by hyperexcitability and continuous firing of the peripheral nerve axons that activate the muscle fibers. It includes progressive muscle stiffness, continuously contracting or twitching muscles (myokymia), cramping, increased and delayed muscle relaxation and sweating. These events tend to persist during sleep or when subjects are under local or general anesthesia. Onset is between ages 15 and 60 years, with most individuals experiencing symptoms before age 40. Stiffness is most prominent in the limb and trunk muscles, although symptoms may be limited to cranial muscles. It is characterized by rippling painful muscle spasms (which, contrary to those seen in the Stiff Person syndrome, persist after nerve block, anesthesia and sleep and have typical electromyographic findings) [Figure 1].

Anticonvulsants, including Phenytoin and Carbamazepine, usually provide significant relief from the stiffness, muscle

Case Report
A 40-year-old female presented with the complaint of a feeling of tightness in the right lower limb in 2007. She used to get abnormal posturing of right lower limb with pronounced downward flexion of the foot. This posturing used to be intermittent, painful, lasting for 3–4 h, triggered with walking and movements at the ankle joint. Later, she developed difficulty in bending the right knee as well. Her gait was deliberate and slow. Her husband noticed absence of leg posturing while she was asleep. She complained of decreased sleep and apprehension about the ailment. She had been treated with antidepressants and antipsychotic medications. She did not respond to medications and, subsequently, her symptoms worsened with stiffness spreading to the other limb, abdomen and neck. She started getting episodes of painful contractions of both lower limbs and abdominal muscles in response to unexpected stimuli such as noise, touch or emotional stress. She became bedridden over the next few months. Two years into the illness, she was diagnosed as having brittle diabetes mellitus, which was insulin dependent, with severe fluctuations of blood sugar levels. No other significant past medical or surgical history was noted. Her family history was not contributory. On examination, her vitals were stable and the lower limbs and trunk were tight to palpation. Paraspinal muscles were hypertrophied. She had normal strength, right foot dystonic posturing and no other extrapyramidal or pyramidal tract signs.

Thus, the main clinical findings were stiffness in the limbs and trunk and painful spasms triggered with sudden stimuli or movement. This raised the following differential diagnosis. Conditions like strychnine poisoning can have a similar constellation of symptoms, but it is acute in onset and very rapid in progression. After exposure 10–20 min later,
spasms and pain associated with Isaac’s syndrome. Plasma exchange may provide short-term relief for individuals with some forms of the acquired disorder.[3] Our patient's symptoms resemble this description to a large extent; however, the symptoms tended to disappear in sleep. The stimulus sensitivity seen in our patient was also unusual for the diagnosis.

Satoyoshi syndrome
It is an uncommon progressive disorder probably of autoimmune etiology, characterized by painful muscle spasms, alopecia, diarrhea and endocrinopathy such as amenorrhea and secondary skeletal abnormalities. Onset is between the age of 6 and 15 years. Disease presents with muscle spasms in the legs and alopecia[4] [Figure 2].

The spasms are painful and progressive, with the frequency varying up to 100 per day, each episode lasting a few minutes. The spasms usually spare the facial muscles. Diarrhea occurs in the first 2–3 years, with intolerance to carbohydrate and high-glucose diets. When the patient is in the attack-free period, nonstimulus-sensitive myoclonus can occur in the arms, legs and neck. It may be associated with endocrinial abnormalities such as amenorrhea and hypoplasia of the uterus. Affected children fail to attain height after 10–12 years of age. They develop bony deformities like genu varus/valgus, lumbar lordosis, etc.[4,5] Our patient was older and did not have any manifestations outside the nervous system.

Stiff person syndrome
A rare neurological disorder characterized by fluctuating muscle rigidity in the trunk and limbs and a heightened sensitivity to stimuli such as noise, touch and emotional distress, which can set off muscle spasms. Electromyography (EMG) studies show the presence of continuous motor activity in both agonist and antagonist muscles.[6] In our patient, the clinical features of stimulus-sensitive spasms that were absent in sleep favored the diagnosis.

Investigations
Routine hematological investigations were normal. Erythrocyte sedimentation rate (ESR) was 7 mm/h. Blood sugars were fairly controlled. Creatine phosphokinase CPK (total) levels were normal. Magnetic resonance imaging of the brain and spine were normal. Her EMG studies showed presence of continuous motor activity, suggestive of Stiff Person syndrome [Figure 3].

Her anti-GAD antibody was negative. Patient's work-up for malignancy, including computed tomography chest and abdomen and tumor markers (CA 125, AFP and CEA) was negative. Clinical history and investigations excluded tetanus, both acute and chronic, and strychnine poisoning and favored the possibilities of Stiff Person syndrome, Satoyoshi syndrome and neuromyotonia.

The patient was started on diazepam therapy, which provided definite but short-term symptomatic relief. In 2009, she developed exacerbation of spasmodic attacks ultimately leading to respiratory failure. The patient required ventilatory support. She was given a trial of IV-Ig 20 g/day for 5 days. She showed significant improvement in her symptoms. She could be weaned off the ventilator over the next 10–12 days, and became ambulatory over the next 6 weeks.

The patient enjoyed a symptom-free period of 1.5 years with occasional episodic exacerbations. However, since January 2011, her spasms increased in frequency. Her suffering progressed till June 2011, to an extent of severe functional disability because of pronounced tightness in the limbs and trunk. She was evaluated again. HbA1c 8.6%. Anti-GAD antibody titer was strongly positive, which was >2000 IU/ml (n <10 IU/ml). EMG showed continuous motor unit activity. Anti-TPO antibody titer was elevated substantially, being 882.86 units/ml (n < 5.08 units/ml). The patient was again given IV-Ig this time as well. She showed significant improvement. She was put on Diazepam 40 mg/day with baclofen 60 mg/day. She continues to remain well till date.
**Final diagnosis**

**Stiff person syndrome**
In 1956, Moersch and Woltmann coined the term **Stiff Man syndrome**. Stiff Person syndrome is a rare neurological disorder characterized by fluctuating muscle rigidity in the trunk and limbs and a heightened sensitivity to stimuli such as noise, touch and emotional distress, which can set off muscle spasms.\[^{6,10}\] It usually starts in the axial muscles and extends to the proximal limb muscles, but the severity of the limb muscle involvement may overwhelm the axial muscle involvement (Stiff Limb syndrome).\[^{7}\]

Females are relatively more affected than males. Age of onset varies from infancy to elderly age group. No genetic linkage is yet known. It is frequently associated with other autoimmune diseases such as diabetes (45–50%), thyroiditis, vitiligo and pernicious anemia. Association of epilepsy, breast cancer and cerebellar ataxia has also been reported.\[^{8}\]

The cause of the Stiff Person syndrome is unknown; however, an autoimmune pathogenesis is suspected because of: (1) the presence of antibodies against glutamic acid decarboxylase (GAD), the rate-limiting enzyme for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid [GABA], (2) the association of the disease with other autoimmune conditions, (3) the presence of various autoantibodies and (4) a strong immunogenetic association. Anti-GAD antibodies, which are found in high titers in most patients, seem to be directed against conformational forms of GAD.\[^{9}\] In our patient, the initial negativity of anti-GAD antibody in the symptomatic stage is curious. New evidence suggests that these antibodies may be pathogenic because they interfere with the synthesis of GABA. In addition, a reduction in brain levels of GABA, which is prominent in the motor cortex, has been demonstrated with magnetic resonance spectroscopy in patients with the Stiff Person syndrome.\[^{9}\]

**Clinical features**

**Early stage**
It usually involves the axial muscles, first complaining of backache and stiffness that gets worse with stress. There is disturbed sleep transition from rapid eye movement to non rapid eye movement REM-NREM. Brief episodes of dramatic worsening are common. At this stage, patients are often diagnosed to have either Fibromyalgia or are labeled psychogenic, as happened in our patient.\[^{10}\]

**Late stage**
Later, the disease involves the proximal limbs. Spasms are stimulus sensitive. There is exaggerated lumbar lordosis and upright posturing with contraction of abdominal muscles. This spasmodic restriction causes extreme depression, which leads to severe impairment in the social functioning.\[^{10}\]

**End stage**
Eventually, facial and pharyngeal muscles get affected but trismus is absent. Joint deformities and skeletal fractures are quiet common. There is increased incidence of postsurgical hernia.\[^{10}\]

One variation of the disease, known as Stiff Limb syndrome, is observed more frequently in patients with diabetes mellitus. In this variation, the axial involvement is less marked and one (or rarely) more extremities are affected.\[^{7}\]

In the Stiff Baby syndrome, distal findings may be more pronounced than in adults. Smaller babies may have increased tonic extension of the leg at the hip. Younger patients frequently have a more pronounced response to startle than adults, and hyperekplexia must be considered in the differential diagnosis.\[^{6,10}\]

**Pathophysiology**

Spinal interneurons function to inhibit spontaneous discharges from the spinal motor neurons, primarily through the action of glycine. However, this is only one inhibitory input for the motor pathway that includes GABA-mediated inhibition from the cortex, brain stem and cerebellum. If GAD function is inhibited significantly, then GABA available for these functions is decreased and muscles become continuously stimulated by the motor neurons. The loss of GABAergic input into the motor neurons is thought to produce the tonic firing of motor neurons at rest and lead to their excessive excitation in response to sensory stimulation.\[^{11}\] Additional possible pathophysiologic etiologies in patients negative for GAD antibody include postsynaptic elements such as synaptophysin, amphiphysin, gephyrin and GABA-transaminase. The main autoantigen of the paraneoplastic form of Stiff Person syndrome is amphiphysin. In about 80% of the subjects with Stiff Person syndrome, disorder develops as nonparaneoplastic phenomenon in association with diabetes mellitus and polyendocrinopathy, often with antibodies to GAD.\[^{9}\]

**Antibodies**

Up to 65% of the patients may have antibodies against the two isoforms of GAD, GAD-65 and GAD-67. Because GAD is also present in the pancreatic cells, serum specimens from patients with the Stiff Person syndrome who are positive for anti-GAD antibodies also stain the β cells of the pancreas. Low titers of anti-GAD antibodies are detected in patients with type 1 diabetes, and up to 30% of patients with the Stiff Person syndrome also have diabetes. In contrast to patients with type 1 diabetes, the antibodies in patients with the Stiff Person syndrome seem to be against the conformational forms of GAD-65 and GAD-67, and recognize the denatured GAD-65 on Western blot assay. Differences in epitope specificity may explain why the incidence of the Stiff Person syndrome in persons with diabetes is low (about 1 in 10,000 persons).\[^{11}\]

In the paraneoplastic form, the stiffness is mostly in the proximal muscles and precedes the detection of the tumor. The most common tumor seems to be breast cancer. Patients with paraneoplastic cases of the Stiff Person syndrome do not have antibodies against GAD, but have antibodies against amphiphysin, another neuronal protein (molecular weight, 128 kDa) that is localized in neurons and synaptic vesicles.\[^{12}\]

**Treatment**

Initial medical treatment may involve GABA-enhancing agents such as baclofen, benzodiazepine or gabapentin. Diazepam at 20–400 mg/day is the most potent symptomatic treatment. Clonazepam, valproic acid, clonidine, vigabatrin (which decreases catabolism of GABA) and tiagabine (which
interferes with uptake of GABA) have also been reported to be effective.\[8,10\]

**Plasmapheresis**

In some patients, plasmapheresis has been demonstrated to be of clinical utility in the treatment of Stiff Person syndrome. No real prescribed dosage exists for plasmapheresis. A five-treatment series administered every other day is considered a standard regimen for autoimmune diseases, but longer and shorter regimens have also been used.\[13,14\]

**Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) has also been used in the inpatient setting for the treatment of Stiff Person syndrome. The usual dose is 2 g/kg, administered over 2-5 days.\[13\]

**Intrathecal baclofen therapy**

Some patients may be candidates for intrathecal baclofen therapy for long-term treatment. Because symptoms may be variable, an externally programmable pump may be the best option. Baclofen pump therapy should not be considered the sole therapy for the disease. It may be fatal if not meticulously supervised.\[15\]

**Monoclonal antibody**

Rituximab therapy has resulted in long-lasting remissions. Clinical trials of this treatment have been completed.\[16\]

Treatment of the tumor and use of corticosteroids may improve the paraneoplastic form. Physical therapy and occupational therapy are critical to the recovery of the patient under treatment.\[17\]

**Prognosis**

Patients with Stiff Person syndrome usually respond well to muscle relaxants, and their condition can stabilize after months to years of progression. Those with Stiff Limb syndrome have a poorer prognosis, as they do not respond well to medications. These patients often require a wheelchair. Prognosis is variable from person to person.\[6,7,10\]

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