Turkish Journal of Neurology

Turk J Neurol 2024;30(1):56-61
Doi: 10.55697/tnd.2024.51

CASE REPORT

Glutamic acid decarboxylase antibody-related stiff person syndrome: Two case reports of a child and an adult

Glutamik asit dekarboksilaz antikoru ilişkili stiff person sendromu: Çocuk ve erişkin iki olgu sunumu

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ABSTRACT

Stiff person syndrome (SPS) is a disease characterized by rigidity in the extremities, axial muscles, and abdominal muscles, severe and painful spasms, and accompanying gait disturbances. Stiff person syndrome is most common in adults between the ages of 20 to 50 and in female sex. The most frequently reported antibody in patients with SPS is antibodies developed against glutamic acid decarboxylase enzyme. In this article, two SPS cases from different age groups who presented with gait disturbance and painful spasms and were found to have glutamic acid decarboxylase antibody positivity were reported with clinical and electrophysiological findings in the light of the literature. As in our cases, SPS should be considered in the differential diagnosis of patients of all age presenting with muscle stiffness and spasms, specifically those that increase with stimulus.

Keywords: Electrophysiological findings, glutamic acid decarboxylase, stiff person syndrome.

ÖZ

Stiff person sendromu (SPS) ekstremite, aksiyel ve abdominal kaslarda rijidite, şiddetli ve ağrılı spazmlar ve yürüyüş bozukluğunun eşlik ettiği bir hastalıktır. Stiff person sendromu, en sık erişkinlerde, 20-50 yaş arasında ve kadın cinsiyette görülmektedir. Stiff person sendromu saptanan hastalarda en sık bildirilen antikor glutamik asit dekarboksilaz enzimine karşı gelişen antikorlardır. Bu makalede yürüyüş bozukluğu, ağrılı spazmlar ile başvuran ve glutamik asit dekarboksilaz antikor pozitifliği saptanan farklı yaş gruplarından iki SPS olgusu klinik ve elektrofizyolojik bulgular literatür eşliğinde sunuldu. Olgularımızda olduğu gibi kaslarda sertlik ve özellikle uyaranla artan spazmlar ile gelen her yaş grubundan hastanın tanısında mutlaka SPS düşünülmelidir.

Anahtar sözcükler: Elektrofizyolojik bulgular, glutamik asit dekarboksilaz, stiff person sendromu.

Stiff person syndrome (SPS) is a disease characterized by rigidity in the extremities, axial muscles, and abdominal muscles, severe and painful spasms, and accompanying gait disturbances. This rare disease has an incidence of 1/1,000,000 and an estimated prevalence of 1-2/1,000,000.[1] Stiff person syndrome is two to three times more common in females. Although it is most frequently observed in adults between the ages of 20 to 50, it has also been reported in children and adolescents in the literature.[1,2]

Stiff person syndrome was first described in 1956 by Moersh and Woltman[3] in 14 patients presenting with difficulty in walking, falls, and accompanying fluctuating, progressive rigidity and painful muscle spasms. Over time, variant forms of this syndrome, such as paraneoplastic SPS, stiff limb syndrome, and progressive encephalomyelitis with rigidity and myoclonus, have been identified.[4] The most commonly reported antibody in patients diagnosed with SPS is against glutamic acid decarboxylase (GAD) enzyme, accounting for 70 to 80% of cases.

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Received: April 18, 2022 **Accepted:** June 22, 2022 **Published online:** March 26, 2024
Cite this article as: Güllü G, Oguz-Akarsu E, Karlı N, Okan MS, Erer S. Glutamic acid decarboxylase antibody-related stiff person syndrome: Two case reports of a child and an adult. Turk J Neurol 2024;30(1):56-61. doi: 10.55697/tnd.2024.51.

Specific antibodies such as anti-glycine (10%), anti-amphiphysin (5%), and anti-DPPX have also been detected in SPS.[5] Additionally, 5 to 10% of cases have been reported as a paraneoplastic syndrome.[1] The presence of another autoimmune disease, primarily type 1 diabetes mellitus (DM), should increase the suspicion of SPS in patients with clinical symptoms.[1,4]

The diagnosis of SPS is based on the criteria established by Dalakas[6] in 2009: *(i)* rigidity in the extremities and axial muscles, particularly in the abdominal and thoracolumbar paraspinal muscles; *(ii)* cocontraction in agonist and antagonist muscles, both clinically and electrophysiologically; *(iii)* episodic spasms triggered by tactile stimuli, sudden sounds, or emotional stress; *(iv)* exclusion of other neurological diseases that could cause rigidity and muscle stiffness; *(v)* detection of anti-GAD antibody (or anti-amphiphysin) positivity through quantitative tests [radioimmunoassay or enzyme-linked immunosorbent assay (ELISA)] or qualitative tests (immunohistochemistry, Western blot, or cell-based assays).

This study reports two patients from different age groups who presented with difficulty in walking, stiffness in the lower extremities, and pain complaints and were diagnosed with SPS.

CASE REPORT

Case 1– A 65-year-old female patient presented to the clinic with severe, painful muscle contractions in the lower back and legs and progressive difficulty in walking. Approximately three years ago, the patient began experiencing back pain and sought treatment from physical therapy and orthopedics clinics. Muscle contractions started accompanying the patient's back pain, which gradually intensified and started to spread to the legs. When presenting to our clinic, the patient was unable to sit due to intermittent and severe muscle contractions in the lower back and legs. Neurological examination revealed axial rigidity, marked spasticity in the lower extremities, increased muscle tone, and hyperactive deep tendon reflexes. The patient could stand only with the support of two people. During the examination, a significant increase in painful muscle contractions was observed due to the patient's anxiety. The Modified Rankin Scale (MRS) score was 4. The patient's medical history included hypertension. There was no significant family history. The patient was on medication with baclofen 90 mg/day and gabapentin 1800 mg/day. Routine biochemistry, complete blood count, thyroid function tests, vasculitis, infection, and tumor markers were within normal limits. A cerebrospinal fluid sample could not be obtained due to the patient's stiffness and hyperlordosis. While cranial magnetic resonance imaging (MRI) was normal, spinal MRI revealed a significant increase in lumbar lordosis. Nerve conduction studies with electromyography (EMG) were normal. Needle EMG examination of the lower extremity muscles, rectus abdominis, and paraspinal muscles showed spontaneous motor unit potential (MUP) discharges and simultaneous cocontractions in agonist and antagonist muscles. Notable afterdischarges following M waves were observed in the tibial F waves study. Cutaneous silent periods in the upper and lower extremities were usual (Figure 1). The autoimmune encephalitis (NMDAR, AMPA1, AMPA2, CASPR2, LGI1, and GABARB1) and paraneoplastic panel [amphiphysin, CV2, PNMA2 (Ma2/Ta), Ri, Yo, Hu, Recoverin, SOX1, Titin, Zic4, GAD65, Tr (DNER)] examined by indirect immunofluorescence assay was strong positive (+++) for anti-GAD. The patient was diagnosed with classic SPS associated with anti-GAD antibodies. Thorax and abdominal computed tomography scans, breast ultrasonography, and whole-body positron emission tomography (PET) conducted for the patient's cancer screening did not reveal any significant features. Steroid therapy was not considered as bone densitometry indicated a high risk of fracture. Diazepam 20 mg/day was initiated, and a slight decrease in muscle contractions was observed. The MRS score was 3 after plasmapheresis (five doses every other day), and the patient was able to move with the aid of a single cane. As the patient did not sufficiently improve with plasmapheresis, an initial loading dose of intravenous immunoglobulin (IVIG; 2 g/kg/5 days) followed by maintenance therapy (1 g/kg/month) for a year was administered. The patient's MRS score was 1 at the end of the year.

Case 2– A nine-year-old male patient presented to our clinic with complaints of muscle contractions in both legs and inability to walk. Patient history revealed that muscle contractions in the left leg started two days ago and that the patient suddenly fell while descending stairs, remained conscious during the fall, and then experienced difficulty in walking due to pain in the back and leg. The patient was examined in the emergency department for trauma, had an X-ray, and was sent home with analgesics. The following day, the patient presented to us with complaints of muscle contractions in both legs and inability to walk. The patient was learned to have type 1 DM for one year with

no regular follow-up or treatment. There was no significant family history. In the neurological examination, there were spasms and tightness in the muscles of both legs that increased with touching, as well as tenderness and axial rigidity in the lumbar region. Occasionally, both lower extremities assumed dystonic postures, with severe pain during those times (Video 1). The MRS score was 4, and other neurological examination findings were unremarkable. Muscle contractions in the legs increased when the patient was excited as the healthcare staff entered the room or when the patient wanted to move. Laboratory investigations revealed a creatine phosphokinase (CK) level of 1447 IU/L (upper limit: 210 IU/L). Complete blood count, thyroid function tests, and vasculitis, infection, and tumor markers were within normal limits. Initially, a potential spinal trauma was considered, and spinal and cranial MRI was performed, which was evaluated as normal. An electroencephalography was conducted suspecting focal seizures and it was reported normal. A cerebrospinal fluid examination could not be performed since the patient could not be appropriately positioned due to severe muscle contractions and axial rigidity. In the EMG examination, spontaneous MUP discharges and cocontractions in the lower extremity muscles were observed. The anti-GAD antibody level in the blood examined by ELISA was 1000 IU/mL (upper limit: 5 IU/L), and the patient was with SPS. Since the maximum dose of baclofen (60 mg/day) did not yield a response, treatment was supplemented with clonazepam. The patient was given immunomodulatory treatment with 0.5 mg/kg of intravenous methylprednisolone for five days with close glucose monitoring, which ranged from 47 to 264 mg/dL. The patient, who benefited from medical treatment, had his spasms resolved and became mobilized within a week, reducing the MRS score to 1. The patient was discharged for outpatient follow-up. The patient fully recovered (MRS: 0) over three years of follow-up, and treatments with baclofen and clonazepam were gradually discontinued.

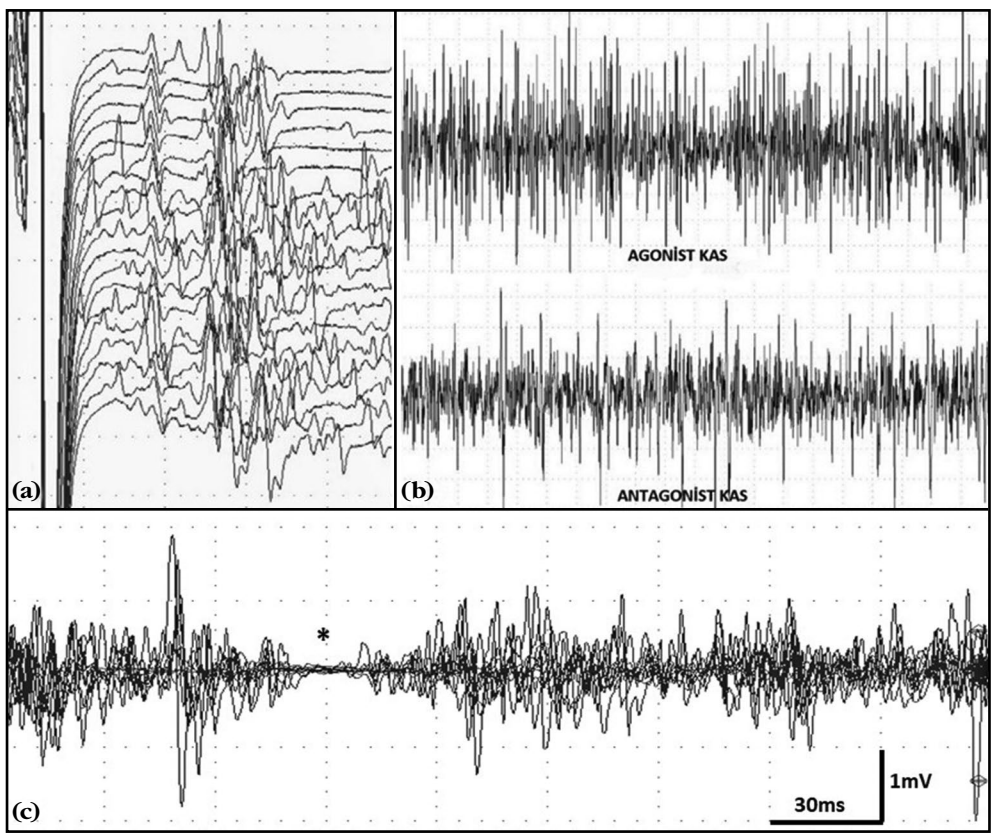
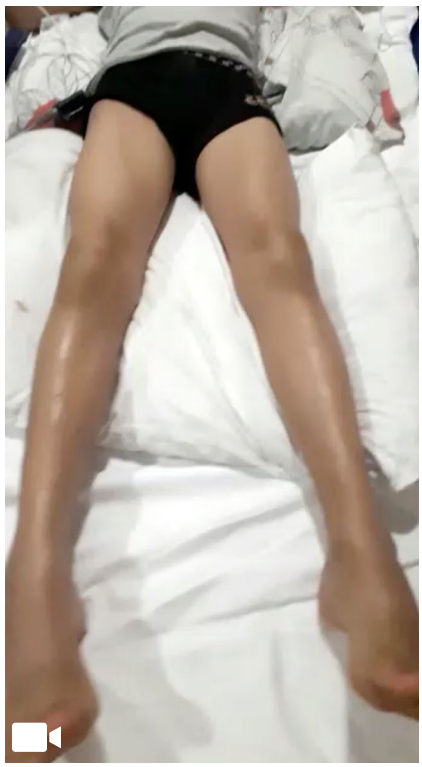


Figure 1. **(a)** Afterdischarges following M waves were observed during the recording of the tibial F waves study. **(b)** Cocontractions observed in the gastrocnemius muscle (agonist muscle) and the tibialis anterior muscle (antagonist muscle) during plantar flexion of the ankle. **(c)** Cutaneous silent period recorded in the lower extremity.



Video 1. Episodic spasms intensified by tactile stimuli.

DISCUSSION

Stiff person syndrome is a rare and easily overlooked syndrome with low awareness.[1] Muscle stiffness, spasms, particularly in axial and lower extremity muscles, and the increase of these spasms with tactile, auditory, or emotional stimuli are typical findings.[2,4] Pediatric SPS often exhibits a clinical phenotype similar to that of adults. Painful spasms, axial and lower extremity rigidity, hyperreflexia, and spasticity are the most common symptoms on admission.[7] Classic SPS generally has an insidious onset. Continuous contraction of agonist and antagonist muscles leads to increased tone and rigidity. Lumbar hyperlordosis is a characteristic posture abnormality. Besides muscle spasms, some patients also experience muscle pains.[1] The episodic and painful muscle spasms can sometimes be so severe that they may cause muscle breakdown, resulting in elevated CK levels. There are even some cases of rhabdomyolysis reported in the literature.[8,9] The elevated CK level in our pediatric case is thought to be related to severe muscle spasms.

The two cases from different age groups demonstrate that SPS should be considered in the differential diagnosis across all age groups. Pediatric SPS, although very rare, constitutes 5% of all SPS cases.[4] In a study of 15 cases with symptoms starting in childhood, a diagnosis was made in adulthood in nine (60%) cases.[7] In the study by Yeshokumar et al.,[7] the median time to diagnosis in the pediatric age group was 6.2 years (range, 1 to 18 years), while in the study by Clardy et al.,[2] the median time to diagnosis was reported as 14 years (range, 0 to 46 years). In adults, the median duration from symptom onset to diagnosis is reported as 6.2 years.[10] We believe that the acute onset of clinical symptoms and early neurological assessment facilitated the diagnosis in our pediatric case, whereas in our adult patient, consultations to nonneurological clinics due to the predominance of pain led to a delay in diagnosis.

The etiology of SPS is unknown, but its association with autoimmune diseases suggests the role of autoimmune mechanisms.[1] Type 1 DM, celiac disease, Hashimoto's thyroiditis, Graves' disease, and myasthenia gravis are frequently reported in these patients.[1,5,11] Furthermore, low titers of anti-GAD are synthesized in type 1 DM and hypothyroidism, but they do not cause a neurological disease. In SPS, anti-GAD levels are on average 50 times higher, while in type 1 DM, there is an average increase of about 10 times.[12] Threshold values for pathological anti-GAD ratios causing neurological disorders have been established: above 2000 U/mL with a radioimmunoassay, above 1000 IU/mL with ELISA, and strong positivity in immunohistochemistry.[13] In our second case presenting with type 1 DM, the anti-GAD level was found to be 100 times higher using ELISA; in our adult case, strong positivity was obtained with the immunohistochemistry method.

Anti-GAD-positive paraneoplastic SPS constitutes 4 to 6% of anti-GAD-positive SPS cases. Particularly in adults, paraneoplastic anti-GAD-positive SPS was reported during the course of malignancies such as thymoma, breast, kidney, thyroid, and colon cancers.[13] Therefore, our patients were screened for malignancy, and no significant findings were detected.

Electrophysiological findings have a significant place in diagnosis and differential diagnosis. Needle EMG examination showing spontaneous MUP discharges at rest and cocontraction of agonist and antagonist muscles are typical findings that indicate a disruption in inhibition in SPS. As observed in our first case, the observation of afterdischarges following the M waves is another finding that helps demonstrate peripheral nerve hyperexcitability.[14] Stiff person syndrome can be

confused with tetanus due to clinical and EMG findings, often leading to misdiagnosis. Obtaining a cutaneous silent period in the EMG examination is an important finding that distinguishes SPS from tetanus.[15] An EMG is also instructive in excluding other neuromuscular disorders resembling SPS. The absence of denervation potentials, myotonia, myokymia, complex repetitive discharges, and the presence of motor unit potentials with normal morphology and firing rate are features distinguishing it from myotonic disorders, myopathy, and neuromyotonia.[16] Particularly in dystonias affecting axial muscles, the stiffness in muscles and postural abnormality become pronounced while walking and decrease when lying supine. Demonstrating dystonic activity in EMG is important. The absence of a significant family history moves away from diagnoses of hereditary spastic paraplegia and hyperekplexia. Moreover, imaging methods are quite useful in the differential diagnosis of diseases such as progressive multiple sclerosis, myelopathy, tumors, and arteriovenous malformation that affect the spinal cord and cause tonic spasms and segmental rigidity.[1]

In treatment, benzodiazepines (diazepam, clonazepam) are the first choice. Steroids, plasmapheresis, and IVIG are recommended as the primary immunomodulatory treatment options. In adults, steroid therapy is initially recommended as methylprednisolone 500 to 1000 mg/day for three to five days, followed by maintenance with prednisone at a dose of 1 mg/kg; however, there is no specific recommended steroid dose for children. The response to medical treatment can vary greatly. For cases resistant to first-line immunomodulatory treatments, rituximab therapy is recommended.[1,10,17] The first case had significant improvement with plasmapheresis and IVIG therapy after not significantly benefiting from baclofen and diazepam. In the second case, no response was obtained from baclofen, but complete recovery was observed after treatment with clonazepam and methylprednisolone.

There is insufficient data in the literature regarding the impact of early diagnosis and treatment on the disease prognosis. In the second case, complete recovery was achieved with early diagnosis and treatment. In the first case, the diagnosis was delayed, there was insufficient response despite plasmapheresis and symptomatic treatments, and significant improvement was observed with IVIG therapy. This suggests that timely diagnosis and early treatment can improve the course of the disease.

In conclusion, SPS should always be considered in the differential diagnosis for patients of any age group presenting with muscle stiffness and spasms, particularly those that increase with stimuli. The possibility of accompanying malignancies and autoimmune diseases should be kept in mind and investigated. Early and accurate diagnosis can help delay the progression of the disease, reduce morbidity, and improve treatment response.

Patient Consent for Publication: A written informed consent was obtained from the first patient and the parent of the second patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Consept, design, literature review, writing the article: G.G., E.O.A., S.E.; Control/supervision: E.O.A., S.E., N.K.; Data collection and/or proccessing: G.G., E.O.A., M.O.; Analysis and/or interpretation: G.G., E.O.A., S.E., N.K., M.O.; Critical review: G.G., E.O.A., N.K., S.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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