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Letter to the Editor

Moersch-Woltman Syndrome - An Uncommon Conundrum

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Pitliya A (2023) reported a case of Moersch-Woltman syndrome (MWS) or Stiff person syndrome (SPS) associated with anti-glutamic acid decarboxylase antibodies (GAD65 antibodies) in a 57-year-old woman with antecedent of depression, who presented muscle spasms mainly involving the neck, shoulders, and upper back, progressively evolving for near two decades, but reduced after utilizing clonazepam and baclofen.[1] Worthy of note was the extensive polypharmacy that she had previously employed without success, and a significant adverse impact on daily normal activities, resulting in a gradual worsening in her quality of life. [1] Neither dystonia, multiple sclerosis, myelopathy, neuromyotonia, Parkinson's disease, primary lateral sclerosis, spinocerebellar ataxia, nor evidence of a paraneoplastic component was detected in this MWS. [1] The authors highlighted the major role of a high index of suspicion for MWS to early establish the correct diagnosis, contributing to prompt adequate management, which is mandatory to propitiate the best outcome.[1]

In this setting, the objective of the following comments on additional novel literature data is to enhance the awareness of the non-specialists about the cornerstone issues related to this very challenging condition.[2-5] Chia NH *et al.*, reviewed data of 173 people with diagnosis or suspicion of MWS between July 2016 and June 2021, based on high titers of GAD65-IgG, glycine-receptor-IgG or amphiphysin-IgG, and/or electrodiagnostic findings and detected 48 (27.75%) with confirmed MWS by GAD65-IgG (68.29%), glycine-receptor-IgG (29.26%), and amphiphysin-IgG (4.87%); while the other 125 cases (72.25%) were the non-MWS patients.[2] The MWS group had more exaggerated startle (81% vs. 56%), unexplained falls (76% vs. 46%), autoimmunity (50% vs. 27%), hypertonia (60% vs. 24%), hyperreflexia (71% vs. 43%), hyperlordosis (67% vs. 9%), and electrodiagnostic changes (74% vs. 17%); besides better response either to benzodiazepines (51% vs. 16%) or to the immunotherapy (45% vs. 13%), and less probability of functional neurologic signs (6% vs. 33%).[2]

The authors highlighted the risks of misdiagnosis that were threefold more common than confirmed MWS, at least in part due to the lack of consensual guidelines for correct management and suggested the respective diagnostic criteria. These included: 1) Symptoms [1 of 2] a. Stiffness (axial regions, limbs, or both), and b. Episodic spasms (axial regions, limbs, or both) triggered by noises, tactile stimuli, or emotional stress; 2) Signs during the symptomatic phase of illness [1 of 3] a. Increased muscle tone (axial or limb), b. Exaggerated lumbar lordoses, and c. Concurrent stiffness of lumbar paraspinal and abdominal muscles; 3) Serological findings [1 of 3] a. High-titer GAD65-IgG in the serum or any positive titer in CSF, b. Glycine-R-IgG in serum and/or CSF, and c. Amphiphysin-IgG in serum and/or CSF; 4) Electrophysiological studies [1 of 3] a. Inability to relax paraspinal muscles in needle EMG, b. Exaggerated acoustic or exteroceptive responses by surface EMG, and c. Co-contraction of agonist/antagonist muscles by EMG; and 5) Exclusion of alternative diagnosis. Definite: all (1–5), probable: at least one of 1 or 2 and 3 and 5 (seropositive), or 1, 2, 4, and 5 (seronegative).[2]

Kamaleshwaran KK *et al.*, reported a 64-year-old woman with difficulty walking due to pain along with muscle rigidity in the bilateral lower extremities, and the diagnosis of MWS was confirmed by GAD65-IgG high levels. [3] She underwent imaging studies which ruled out the hypothesis of a paraneoplastic etiology for the MWS, but the 18F-FDG PET scan showed bilateral thalamic hypometabolism, and she improved by the rituximab use; worth of note was the highly hypermetabolic symmetric muscle uptake in total body with fasting for 6 hours.[3] The authors stressed that MWS should be added among abnormal muscle uptake in FDG PET/CT studies.[3]

Matsui N *et al.*, identified 30 cases of MWS GAD65-positive in Japan from January 2015 to December 2017; four patients had glycine-receptor-IgG, and one patient had both GAD65 and glycine-receptor-IgG positive.[4] The estimated prevalence of MWS was 0.11 per 100,000 population, the average age at onset of disease was 51 (26-83) years, 76% were women, and 70%

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presented with the classic manifestations of the syndrome. [4] The time from symptom onset to diagnosis was longer in the GAD65-IgG high-titer group (13 vs 2.5 months); the coexistence of diabetes mellitus and the lack of long-term immunotherapy were factors of poor outcome, and authors stressed the need for more aggressive immunotherapy in GAD65-positive patients with MWS.[4]

Perri M *et al.*, reported a 47-year-old male with difficulty walking, muscle spasms, stiffness in lower limbs, and panic attacks, who was misdiagnosed myasthenia gravis two years ago because of muscle weakness.[5] He was prescribed pyridostigmine, vilazodone, and clonazepam without control of the clinical manifestations, and presented alteration in the gait, prostration, and frequent falls; had hypertonic muscles in all the extremities, besides hyperreflexia, spasticity, and clonus in the lower limbs, and a slow march with an increased base.[5] With diagnosis of MWS GAD65-positive, IV gamma globulin was given 6 days and diazepam was titrated accordingly; thoracic images showed a mediastinal nodule that was excised (type B2 thymoma with 3 x 2 cm); the early postoperative period was with progression of stiffness refractory to increased diazepam doses, but after the pulses of methylprednisolone and IV gamma globulin, he was discharged with improved ambulation.[5] The authors emphasized the exceeding rare association (only 20 reported cases) of MWS with thymoma.[5]

In conclusion, the herein commented studies focused on the role of the early diagnosis and adequate management of the challenging MWS by a multidisciplinary team to avoid underdiagnosis and misdiagnosis. MWS diagnostic criteria include clinical manifestations, physical examination findings, serological and CSF testing, and electrophysiological study; and more aggressive immunotherapies are needed for GAD65-positive.

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