Case report

A SERIES OF CASES WITH PERM IN ASSOCIATION WITH GAD, NMDA, LGI1 AND OTHER ANTIBODIES

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ABSTRACT

Objectives of research: Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe syndrome that presents with autonomic features, hyperekplexia, painful spasms and breathing problems. It is part of the spectrum of the stiff-person syndrome (SPS) with anti-glutamic acid decarboxylase (GAD) antibodies in up to 80% of patients.

Methods: We present a series of 3 cases in The Republic of North Macedonia that were diagnosed as Progressive Encephalomyelitis with rigidity and myoclonus.

Results: A series of 3 cases have been processed, which are diagnosed as Progressive encephalomyelitis with rigidity and myoclonus (PERM). The initial symptoms of the patients were bilateral ataxia, dysarthria, the change of sensations in the area of the feet, moments of forgetting things, unstable posture followed by the involuntary movement of the lower limbs, shaking of the upper limbs. The goal is to show the association of the presence of certain antibodies to the progressive clinical manifestations of the disease itself. Furthermore, all patients were GAD, Hu D and Ri positive. Two were positive for the NMDA antibodies. Only one patient was positive for Anti-CMV, EBV Viral Capsid Antigen-Antibody (VCA) IgG, Anti Herpesvirus VZV IgG, anti-LGI1 antibodies. It is common that all three patients have been given/given series of plasmapheresis and IVIG cycles, but without any significant progress. Unfortunately, one ended up lethal, and the other two are not in an enviable state.

Conclusions: These three cases do not only show the clinical spectrum of PERM, but also the association of this disease with Hu, Ri, GAD, NMDA and LGI1, and other antibodies. This combination of antibodies may be responsible for the progressive character of this disease.

Keywords: PERM, GAD antibodies, NMDA antibodies, IVIG

INTRODUCTION

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe syndrome that presents with autonomic features, hyperekplexia (brainstem myoclonus or excessive startle), painful spasms and breathing problems [1]. This syndrome can present with an insidious onset, as well as an acute or subacute presentation, or exacerbations on a chronic course [2]. Symptoms can be explained by the disruption of the inhibitory glycinergic synaptic transmission, which is prominent in the spinal cord and brainstem [1]. Classical PERM affects women two to three times more often than men. Several classifications have been proposed for SPS according to the severity or distribution of the stiffness, related neurological findings and association with neoplasia [3]. Immunomodulation using corticosteroids, intravenous (IV) immunoglobulin, plasma exchange or cyclophosphamide are described as an effective treatment [4]. Initial diagnosis of PERM is not easy and literature is limited regarding the long-term course of the syndrome.

Here, we report a clinical presentation of PERM in three different patients, with more common moments.

METHODS & MATERIAL

We present a series of 3 cases in The Republic of North Macedonia that were diagnosed as Progressive Encephalomyelitis with rigidity and myoclonus (PERM).

RESULTS

(Case1)

A 49-year-old man was referred to the State Hospital of Neurology in Skopje for bilateral ataxia, changing of sensations in the area of his feet and moments of forgetting things. The difficulties started two months before the reception of the Neurology Clinic. A few days after he was admitted to the hospital, the patient had complete incapability for movement and paralysis of the lower limbs. Meanwhile, deterioration of speech with occasional attacks of confusion and loss of control of urination followed. In addition to this, the surface sensation and deep sensibility for vibrations of the upper and lower limb were lost. The findings from the cerebrospinal fluid tests were in favor of hematoencephalic barrier dysfunction. Also, the EEG examination was dominated by low-voltage, slow wavy activity from theta rank. SEP of n. medianus and n.tibialis showed cortical responses with prolonged latency, bilaterally. This finding is in favor of a defect in the conduction of the central and peripheral paths bilaterally. Moreover, the finding of the magnetic resonance showed that on the level of the foramen magnum, there were punctiform, hypersignal lesions peripherally with restriction of diffusion. Cerebellar, bilateral hyper signal lacunar lesions were found bilaterally. Global, cortical atrophic events also, were observed both frontally and temporally. Besides, small pleural effusions were observed on the chest Echo. Diabetes Mellitus was diagnosed 10 years ago. Therefore, the differential diagnostic was thought to be diabetic polyneuropathy. He was positive to GAD (glutamate decarbox.) and NMDA (N-methyl-D-aspartate) antibodies. The patient had received 1 cycle of IVIG, 2g/kg TT, but without therapeutic effect. Unfortunately, the patient died.

(Case2)

A 38-year-old woman, previously healthy was referred to the State Hospital of Neurology in Skopje for the subacute onset of severe and progressive gait disturbance associated with painful muscular rigidity and spasms of the trunk and lower limbs. Additionally, unstable posture followed by involuntary movement of the right leg appeared. After a short period, there was also the involuntary movement of the left leg with propagation to myoclonic limb jerks with hyperekplexia. Symptoms appeared 4 months before hospitalization with a blurred vision of the left half of the eye field and in few times seizures described like GTCS, but without urination and biting of the tongue. EEG showed theta-delta dysrhythmia, the evoked potential was normal, except SEP of n. tibialis with mildly prolonged latency. Manganese was slightly higher at 1.3 (rr 0.3-1.1), GAD (glutamate decarbox.) antibodies were 33.6 (rr<10) and she was also positive to Hu D and Ri antibodies. Symptoms were partially responsive to baclofen, corticosteroids, and levetiracetam. The patient so far has received 3 cycles of IVIG, and recently a series of a 3 plasmapheresis, but without a marked therapeutic effect.

(Case3)

A 40-year-old man was referred to the State Hospital of Neurology in Skopje because of a condition that previously persisted for a month. Actually, the patient was in a coma, with a characteristic position. Hands were in flexion in the elbows, the palms were in fists. Occasionally there was a shaking of the upper limbs. In addition to this, he had visual hallucinations and did not respond to verbal stimuli. On mechanical irritation, he responded by shaking the upper extremities in the form of myoclonus. The pupils were tightened. The left nasolabial ditch was lowered. In the urine, blood was noticed. Furthermore, cortical reductive changes of diffuse character were detected on the computerized tomography of the head. On the other hand, decreased values of cortisol and ACTH were detected. The performed gas analyzes showed hyposaturation, hypoxemia, and hypocapnia. There was a metabolic acidosis which was compensated by respiratory alkalosis. Meanwhile, the magnetic resonance of the brain showed hypersignal changes at the basal ganglion level, as well as, on the nucleus caudatus. Anti-CMV, EBV Viral Capsid Antigen-Antibody (VCA) IgG, Anti Herpesvirus VZV IgG, anti-LGI1 antibodies, were all positive. He was also positive to GAD (glutamate decarbox.) and NMDA (N-methyl-D-aspartate) antibodies. Myoclonic attacks were registered on multiple occasions. The patient received 3 cycles of IVIG and 3 plasmaphereses, but no

improvement was observed on the neurological and somatic plan.

DISCUSSION

A major breakthrough in our understanding of the pathogenesis of PERM occurred in 1988, when an association between anti-GAD antibodies and PERM was first reported by Solimena et al. 26-GAD is the rate-limiting step in the decarboxylation of L-glutamate to ε-aminobutyric acid (GABA) [5]. Anti-GAD antibodies are 80% positive in patients with PERM. Other antibodies, such as N-methyl-D-aspartate (NMDA) receptor antibodies are associated with the different sub units of the NMDA receptor. Antibodies to the delta or NR2 subunits of the NMDA receptor are associated with limbic encephalitis, systemic lupus erythematosus (SLE), ataxia and epilepsia partialis continua. Antibodies against the NR1, NR2A, and NR2B subunits of the NMDA are found in patients presenting with psychiatric symptoms, amnesia, seizures, dyskinesias, autonomic dysfunction and loss of consciousness [6]. Autonomic instability is a common feature in adults, with about half of patients developing central hypoventilation that generally requires weeks of mechanical support [7]. Most patients have abnormal CSF studies with a lymphocytic pleocytosis. At presentation, about half of the patients have abnormal MRI findings, most commonly increased signal on fluid-attenuated inversion recovery (FLAIR) or T2 sequences in the cerebral or cerebellar cortex or medial temporal lobes. Abnormalities have been reported in other areas, such as the corpus callosum or brainstem [8]. Just over half of patients have an associated tumor, most commonly an ovarian teratoma that can be mistaken for a benign cyst. The detection of a tumor is rare in male patients. Other tumor types in isolated cases include teratoma of the mediastinum, small-cell lung cancer (SCLC), Hodgkin's lymphoma, neuroblastoma, breast cancer, and germ-cell tumor of the testes [9]. Very interesting, anti-LGI1 antibodies is manifesting with memory deterioration, epileptic seizures, mental disorders, and hyponatremia. The hyponatremia is a characteristic feature of anti-LGI1 AE, and 60%~ 88% of such patients have refractory hyponatremia according to the prior studies. The pathogenic mechanism is likely associated with the syndrome of inappropriate antidiuretic hormone secretion causing by the simultaneous LGI1 expression of the hypothalamus and kidney. Our case was consistent with prior reports, with a lower blood level of sodium (119.1 mmol / l) [10]. To sum up, the diagnosis of PERM is difficult to set. EMG, antibodies in serum and CSF could help to confirm the diagnosis. Initial clinical presentation can be very unspecific and uncommon, and this case is no exception. A high level of D-dimers was observed in the three patients. This explains the existing risk of thromboembolism. Meanwhile, common differential diagnoses of PERM syndrome are stiff person syndrome, paraneoplastic SPS and NMS [11]. With respect to immunotherapy, plasmapheresis, intravenous immunoglobulin (IVIG), corticosteroids and rituximab have been reported to be successful in individual cases, although the efficacy of these agents has not been established. In addition, some reports have demonstrated the efficacy of long-term basement azathioprine treatment for SPS spectrum disorders. However, PERM remains an expanding clinical entity that is constantly being enriched with new symptoms and antibodies [12]

CS-corticosteroids, CYS-cyclosporine, GAD-Ab-sglutamicaciddecarboxylase antibodies IVIg intravenous immunoglobulin, PE-plasmapheresis, PERM-progressive encephalomyelitis with rigidity and myoclonus

These three cases do not only show the clinical spectrum of PERM, but also the association of this disease with Hu, Ri, GAD, NMDA and LGI1 antibodies. This combination of antibodies may be responsible for the progressive character of this disease. The plasmapheresis and IVIG cycles did not show significant therapeutic progress. Unfortunately, one of them ended up lethal, and the other two are in a bad sta te..

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Table 1 Summary of clinical features, laboratory findings, and outcome

Patient no.	Case 1	Case 2	Case 3
Age at onset/sex	49/M	38/F	40/M
Diagnosis	Idiopathic PERM	Idiopathic PERM	Idiopathic PERM
Initial symptoms	Bilateral ataxia, changing of sensations in the area of the feet and moments of forgetting things	Unstable posture followed by involuntary movement of the right leg	Shaking of the upper limbs, ataxia, dizartrija
Ocular movements	Horizontal gaze palsy, gaze-evoked nystagmus	Blurred vision of the left half of the eye field	Narrowed pupils
Myoclonus	Moderate	Moderate	Strong
Hyperreflexia	Moderate	Moderate	Moderate
Hyperekplexia	Mild	Moderate	Moderate
Rigidity, spasm, stiffness	Strong	Strong	Strong
Other features	Diabetes mellitus type 2, Diabetic polyneuropathy Hyperlipidemia	Seizures, hypothyroidism	Visual hallucinations Coma
MRI	On the level of the foramen magnum, there were nctiform, hypersignal lesions peripherally with restriction of diffusion.	Complete obliteration of the front subarachnoid space with mild compression on the medulla spinalis	Hypersignal changes at the basal ganglions level, as well as, on the nucleus caudatus
GAD-Abs titer (IU/ml)	32.7	33.6	33.1
Other Abs	Hu D and Ri antibodies, NMDA antibodies	Hu D and Ri antibodies	NMDA antibodies Hu D and Ri antibodies Anti-CMV EBV Viral Capsid Antigen-Antibody (VCA) IgG Anti Herpesvirus VZV IgG Anti-LGI1 antibodies
Treatment	CS CYS 1 cycle of IVIg	3 cycles of IVIg, CS, CYS 3 series of PE	3 cycles of IVIg, CS, CYS 3 series of PE
Outcome (observation periods)	Without therapeutic effect. The patient died.	Initially improved with consecutive relapse.	No improvement was observed on the neurological and somatic plan.

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