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MOVEMENT DISORDER ASSOCIATED WITH CELIAC DISEASE AND THYROID DYSFUNCTION: CASE REPORT

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ABSTRACT:

Autoimmune movement disorders are uncommon yet likely treatable conditions. It is challenging to diagnose and manage these disorders, ultimately leading to a significant morbidity in terms of functional disability of patient. It is troublesome for practicing neurologists to identify whether the antibodies which are detected during the work up of these autoimmune movement disorders are merely incidental or have pathogenic role. This will help them to decide regarding whether to start immunotherapy or not. Here we have discussed two patients of movement disorder who were found to have positive work up for other autoimmune diseases. Available Literature on autoimmune movement disorder is very limited and further research on large scale is needed.

KEY WORDS: Autoimmune movement disorder, autoimmune dystonia, gluten ataxia, celiac disease, thyroid dysfunction

BACKGROUND: Autoimmune movement disorders comprises of a widespread group of neurologic disorders which occur either in isolation or along with more diffuse autoimmune illnesses. The exact incidence and prevalence of autoimmune movement disorders is not known as it's a rare disorder and very limited data is available on it comprising of few case reports or small sample studies. One estimates suggest that all autoimmune diseases combined affect about 3% of the US population, thus approximately 10 million people.¹ Many movement disorders occur due pathologic alterations in the basal ganglia or their connections including caudate, putamen, and pallidum, subthalamic nucleus, substantia nigra, pedunculopontine nucleus, although some exceptions can be present. Due to the fact that pure, isolated autoimmune movement disorders are uncommon, work up for other aetiologies is strongly recommended.² Any movement disorder phenomenology can occur in these disorders and many of the presentations can mimic neurodegenerative disorders, such as Huntington disease. Disorders may be ataxic, hypokinetic (Parkinsonism), or hyperkinetic (myoclonus, chorea, and other dyskinetic disorders^{3,4}.

Movement disorders are commonly detected in autoimmune diseases. Chorea may present in patients with anti-NMDAR encephalitis, Sydenham disease, lupus and anti-phospholipid syndrome. Dystonic seizures and neuromyotonia may precede autoimmune encephalitis. Anti-glycine antibodies are encountered in the pathogenesis of progressive encephalomyelitis presenting with rigidity and myoclonus. Hashimoto's encephalitis and opsoclonus-myoclonus syndrome have commonly tremor and myoclonus. Few case reports and review articles also highlight the association of Celiac disease and autoimmune thyroid disorders with autoimmune movement disorders⁵
⁶. Celiac disease (CD) approximately accounts for up to 10% of neurological manifestations irrespective to the presence of malabsorption symptoms⁷ According to an article published in 2018, in patients with autoimmune disorders affecting the central and peripheral nervous system, movement disorder are frequent. They may be found in autoimmune disorders incited by an infectious agent, like streptococcus in Sydenham's chorea, or in basal ganglia encephalitis with antibodies against the dopamine-D2 receptors. In these scenarios, chorea or dystonia are usually the most prominent. In diffuse or limbic encephalitis with antibodies directed against neuronal cell-surface antigens, patients also have MD. Anti-NMDA receptor encephalitis is one of the most common and may present with a variety of MDs, including: chorea, stereotypies, dystonia and myorhythmia while in stiff-person syndrome or cerebellar ataxia, intracellular enzyme glutamic acid decarboxylase are found most commonly.⁸ Clues of when to suspect an autoimmune etiology are Female patient, Subacute onset, variable course of disease, neurological disease with multiple foci, autoimmunity personal or family history, Patient having history of cancer or suspicion of new cancer, Abnormal laboratory supportive tests, i.e., Cerebrospinal fluid, imaging and the response to immunotherapy.² A rapid diagnosis of an autoimmune disorder is utmost as early therapeutic intervention improves long-term prognosis and

may be life-saving. Treatment usually comprises of some form of immunotherapy and symptomatic therapy of the abnormal movements with dopamine depleters, dopamine receptor antagonists, or GABAergic drugs. Early-initiated immunotherapy leads to the best possible outcomes. Moreover, depending on the antibody profile, a search for cancer may be necessary followed by removal of an underlying tumour for optimal outcome.^{3,4} It is challenging to diagnose such autoimmune disorders due to the delayed clinical suspicion, improper approach to get the relevant systematic work up and lack of facilities for specific antibodies detection or in paraneoplastic cases getting extensive work up for occult neoplasm. The whole work up is expensive and time consuming ending mostly in lost to follow up of patients. For instance, in literature, work up suggested for autoimmune movement disorder include CRMP-5, ANNA-1 (Hu), ANNA-2 (Ri), GAD65, VGCC antibodies for chorea, ANNA-2 (Ri), CRMP-5, NMDA-R, GAD65, DPPX antibodies for myoclonus, NMDA-R for dyskinesia, LGI1, GAD65 for Parkinsonism, GAD65, DPPX, Amphiphysin for Stiff-Person Spectrum Disorders, ANNA-1 (Hu), PCA-1 (Yo), GAD65, VGCC, CASPR2, mGluR1, DPPX for ataxia^{3,4} Despite all these limitations in diagnosis, early management is very important.

CASE 1:

26 years old female patient with no known previous comorbid, married, mother of 2 children up and about till 2 years back. She had history of fever 2 years back which was intermittent, high grade for which she was treated empirically. Fever subsided in few days but she started complaining of difficulty in speech, tremors of neck and upper limbs along with paroxysmal abnormal involuntary twisting and posturing of limbs characterized as dystonic posturing of limbs. Her tremors were characterized as rhythmical oscillatory abnormal involuntary movements of neck in horizontal direction present at rest while with action and intention becomes increased in amplitude and frequency. Her symptoms progressively increased and she started having vertigo and limb and truncal ataxia leading to difficulty in walking. No family history of any neurological disease. Her work up showed Hemoglobin (Hb) 10.6 g/dl (12-15 g/dl) with normal total leukocyte count (TLC) and Platelet count, Erythrocytic sedimentation rate (ESR) 55 mm/1st hour (0-25 mm/hr). Peripheral film showed hypochromia, anisocytosis and poikilocytosis. Thyroid profile repeatedly showed low Thyroid stimulating hormone TSH 0.16 microunit/ml (0.25-4.0 microunits/ml) with normal Free triiodothyronine (Free T3) and Free Thyroxine (Free T4 levels). Patient had complaints of palpitations, weight loss and tremors which favours her thyroid disorder. As she had symptomatic thyroid disorder, possibility of sick euthyroidism is ruled out. Her thyroglobulin autoantibodies and thyroid peroxidase autoantibodies turned out negative. Ultrasound thyroid gland showed slightly enlarged both lobes of thyroid glands with non-homogenous texture. Findings concluded as diffuse goiter most probably associated with thyroiditis. Antinuclear antibodies (ANA) profile (which include ANA, antimitochondrial antibodies (AMA), anti smooth muscle antibodies ASMA) and Anti-double stranded DNA antibodies (AntiDsDNA) were negative. Vitamin B12 level was 626 pg/ml (181-906 pg/ml). Wilson disease work up was negative including serum ceruloplasmin level and 24 hours urinary copper. Creatine phosphokinase (CPK) level normal. Patient had history of occasional diarrhoea and undocumented weight loss for 2 to 3 years. Anti-tissue transglutaminase IgA reactive while Anti tissue transglutaminase IgG non-reactive. MRI brain showed prominence of cerebellar folia and dilatation of fourth ventricle consistent with cerebellar degeneration and atrophy. Repeat MRI brain after 8 months showed re-demonstration of findings of cerebellar atrophy. Patient was started on amantadine 100 mg twice daily, trihexiphenidyl 2 mg twice daily titrated to thrice daily dose, propranolol 10 mg thrice daily, vitamin E 600 mg twice daily and supportive treatment along with rehabilitation including gait training and balancing exercises. Gluten free diet was advised. Endocrinology review was taken for thyroiditis who started prednisolone 1 mg/kg/day. After 4 weeks of follow up patient showed some improvement in her tremors, ataxia and dystonia.

CASE 2:

35 years old male patient of average height and weight presented with continual abnormal involuntary, non rhythmical, non-stereotypical movement of tongue and jaw with some twisting and posturing characterized as oromandibular dystonia, slurred speech consistent with dysarthria, bradykinesia (slowness of movements), and difficulty in walking along with right leg dystonic posturing for last 2 years. No family history of any neurological complaint. He did not use any antipsychotic. No symptoms of hypothyroidism, myopathy and malabsorption were present on detailed history. His work up showed normal Complete blood count (CBC), ESR 5 mm/hr (0-25 mm/hr). TSH 68.90 microunits/ml (0.25-4.0 microunits/ml), FT3 1.93 pg/ml (2.0-4.25 pg/ml), FT4 0.01 pg/ml (7-18 pg/ml) Anti thyroid peroxidase antibodies (Anti TPO) > 1000.0 IU/ml means highly positive (<5.61IU/ml), Vitamin B12 136pg/ml (181-906 pg/ml) which was replaced, vitamin D level 18.0 ng/ml (upto 30 ng/ml), CPK level of 3330 U/L

(male 24 -195 U/L) which on repeat testing found to be 10,400 U/L, anti Transglutaminase IgG 0.304 (cut off 0.304 by ELISA) and IgA 0.316 (cut off 0.212 by ELISA) were positive, Fasting lipid profile serum cholesterol 221 mg% (<200 mg%) LDL 151 mg% (upto 100 mg%). His serum ceruloplasmin 0.29 g/L (male 0.15-0.30 g/L), 24 hours urinary copper 48 ug/day (<60 ug/day), SGPT 32U/L (<40 U/L). ANA was positive. Magnetic resonance imaging (MRI) brain showed prominence of the cortical sulci and ventricles representing brain involution not corresponding to patient's age (figure 1). Patient was on thyroxin 100 ug per day, levodopa/carbidopa 25/250 mg half tablet thrice a day (TDS) and trihexiphenidyl 2 mg half TDS titrated upto 2 mg TDS, Baclofen 10 mg half BD titrated gradually to 1 TDS along with rehabilitation. After a follow up of 4 weeks, his oromandibular dystonia improved to some extent but no significant improvement in his leg dystonia and bradykinesia. Whether patient should be started on gluten free diet as he was asymptomatic for coeliac disease and immunotherapy on the basis of work up or not to improve patient's dystonia was still undecided. According to the available literature patient was planned for immunotherapy with regular follow up of his symptoms for the response.



FIGURE 1: MRI T2W image of case 2 showing prominence of the cortical sulci and ventricles representing brain involution not corresponding to patient's age (Blue arrows). Hyper intense signal are seen in bilateral basal ganglia (Red arrows).

DISCUSSION

Autoimmune movement disorders in neurology are emerging and likewise the associated autoantibodies which need to be worked up. A number of essential tests as the supportive evidence are recommended to be performed in case of suspected autoimmune movement disorder. Antibody-related dystonia differs from primary dystonia, as it follows a characteristic pattern in body parts affected and age at onset. In a patient with adult onset dystonia, secondary causes of dystonia are more common. Work up is needed for the secondary causes which turned out to be autoimmune in origin as our patient had significant abnormalities in work up which suggest a systemic autoimmune involvement. Antibody associated dystonia typically presents as a combined dystonia means in combination with further clinical signs, in particular encephalopathy⁹ Neurodegeneration as evident on MRI brain of my case 2 patient with OMD and limb dystonia is supporting this feature. Moreover he was asymptomatic for celiac disease and thyroid disorder and surprisingly had very high CPK without any evidence of myopathy. American academy of neurology published a small study in 2019 comprising of 4 patients diagnosed with autoimmune dystonia. Generalized asymmetric dystonia was the most common presentation, and parkinsonian symptoms (rigidity and resting tremors) were present in 1 patient. serum and cerebrospinal autoimmune encephalitis work up were inconclusive. All patients were treated with Immunotherapy using intravenous methylprednisolone 1 g daily for 5 days and intravenous immunoglobulin 0.4 gm/kg for 5 days, followed by azathioprine maintenance dose (2 mg/kg). Improvement was found in all cases with complete resolution of autoimmune dystonia in 2 cases. Hence, it was concluded that despite a significant delay in therapy due to misdiagnosis, autoimmune dystonia patients may respond well to immunomodulators with an encouraging outcome¹⁰. Among the disorders associated with autoimmune disease, Celiac disease (CD) is emerging as being frequently reported with significantly increased prevalence in individuals with CD and their first-degree relatives as compared to controls¹¹⁻¹³. The estimated burden of Autoimmune disease (AD) in CD cases up to 15%¹⁰. It has a wide clinical spectrum which includes specific features of malabsorption with diarrhoea, non-specific extra intestinal features, subclinical or asymptomatic variants, and likely disease characterized by positive serology with a normal biopsy of intestinal mucosa^{14,15}. The risk factors for developing other AD are an early diagnosis and a positive family history of autoimmunity, whereas the gluten-free diet (GFD) has a beneficial role¹⁶. Another article concluded that autoimmune movement disorders with an extracellular antibody and without cancer are more likely to respond to treatment while the disorders with a cancer and/or an intracellular antibody respond less well to immunotherapy². Furthermore, while a GFD is found to improve and reverse symptoms of gluten-associated ataxia and is an established therapy for CD, it is not the case with oromandibular dystonia (OMD). CD has been found increasingly in patients with autoimmune thyroid disease i.e. Grave's disease and Hashimoto's thyroiditis, having a 2% to 7% prevalence⁵. Several mechanisms are suggested about the co-occurrence of CD and autoimmune thyroid disease like similar genetic predisposition and both having the gene encoding cytotoxic T-lymphocyte-associated antigen. In addition, tTG2 IgA antibodies has been shown to react with thyroid tissue, leading to the development of thyroid disease in CD. In our both cases patients had positive work up for celiac disease as well as had evidence of thyroid dysfunction along with the movement disorder.

In 2017, "Isolated Neurological Manifestation in Silent Celiac Disease" was published in which a case of idiopathic oromandibular dystonia (OMD) is discussed that was unresponsive to traditional symptomatic therapy. However, complete resolution of symptoms was obtained after celiac disease (CD) diagnosis and gluten free diet⁶. In the same way, our case 1 patient also showed the improvement. Association of asymptomatic high creatine phosphokinase (CPK) level and celiac disease or other neurological illnesses remains unexplained except for the limited clue due to its types CK MM, CK BB, and CK MB. Further studies are highly recommended to clarify the unexplained factors and further management of such cases.

CONCLUSION:

Isolated autoimmune movement disorders are uncommon and are usually associated with other neurological features. A prompt and thorough work up for an underlying cause and associated neural or systemic antibodies in such suspected cases. Ultimately through this approach decisions can be easily taken for the treatment and prognosis of disease. Further studies are direly needed to clarify the issues encountered in management of such cases.

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Ramla Nayaib Hashmi; data collection, data analysis, manuscript writing, manuscript review

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