

Encephalitis and Ocular Flutter Due to an Undifferentiated Connective Tissue Disorder

Sir,

A 30-year-old woman presented to us with fever, chills, and rigor and lethargy of three days duration. She had a history of polyarthritis and fatigue of three years duration. Two months earlier, she had been started on hydroxychloroquine. On examination, she was febrile, drowsy, had neck stiffness, papilloedema, and ocular flutter (OF). [Video 1] Optic nerve sheath diameters were elevated (0.65 mm) bilaterally, suggestive of raised intracranial pressure. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) brain with contrast was normal. Her blood results showed Leukopenia (3,000/uL), thrombocytopenia 147 k/UL, and normal C3, C4 levels. Cerebrospinal Fluid (CSF) showed mild pleocytosis (total count of 28 cells [100% lymphocytes]) and high protein 226 mg/dl with normal glucose levels and an elevated opening pressure of 27 cms H2O. A Biofire meningoencephalitis panel was negative [E. coli, H. influenzae, L. monocytogenes, N. meningitidis, S. agalactiae, S. pneumoniae, CMV, Enterovirus, HSV 1 and 2, HHV-6, human parechovirus, Varicella zoster virus, and C. neoformans/gattii]. Work up for Dengue, Malaria, Scrub Typhus, Leptospira, HIV, and Lyme disease were negative. Rheumatoid Factor (30 IU/mL) and Antinuclear Antibody (ANA) were positive. ANA profile showed very strong bands for nRNP/SM and Ro-52. Anti CCP [<7 U/mL], anti-Beta 2 glycoprotein IGG, IGM, Lupus anticoagulant-DRVVT, Anti-Ds DNA and anti-Cardiolipin antibodies (IgG and IgM) reports were negative. Autoimmune neuronal antibodies [GABA B receptor, Glutamate receptor antibody NMDA (Anti NR-1), Contactin-associated protein 2 (CASPR2), Leucine-rich glioma inactivated protein 1 (LGI1), AMPA 1, and AMPA 2 antibodies], MOG IgG, and NMO IgG were negative. Paraneoplastic antibody panel [ANNA-1, 2, 3, PCA 1, 2, Tr, AGNA-1, Amphiphysin, CRMP-5, Ma/Ta] were also negative. She was started on Inj Dexamethasone 4 mg IV BD \times 5 days and made an uneventful recovery within a week. Subsequently, Mycophenolate mofetil 1 gm/day was added to hydroxychloroquine at discharge.

Our patient fulfilled the criteria for undifferentiated connective tissue disease (UCTD) [Arthralgia, arthritis, a positive ANA result, and a disease duration of three years]. She presented with a short-lasting steroid-responsive encephalitis, specifically a

rhombencephalitis with OF. [Table 1]. Rhombencephalitis refers to inflammatory conditions affecting the hindbrain (brainstem and cerebellum) and is associated with a wide variety of etiologies including infections (predominantly Listeriosis), autoimmune disease, and paraneoplastic syndromes. The detection of OF in our patient localized the condition to the ponto-cerebellar area. We present an unusual case UCTD with OF.

There are five major diffuse connective tissue diseases (DCTD) according to the conventional classification schema: Systemic lupus erythematosus; Systemic sclerosis (scleroderma); Myositis, Rheumatoid arthritis, and Sjögren's syndrome. Apart from these classic five, there are patients who meet the criteria for more than one DCTD, while others exhibit only some of

Table 1: Conditions associated with Opsoclonus-myooclonus syndrome and ocular flutter

Idiopathic (Isolated OF)	Demyelination
Paraneoplastic	Multiple sclerosis
Lung	MOG antibody-associated demyelination (MOGAD) ^[1]
Breast	Metabolic
Neuroblastoma	Hyperosmolar nonketotic coma
Autoimmune	Toxic
NMDA	Serotonin syndrome ^[2]
GAD 65	Cocaine
Ganglioside anti-GQ1b antibodies	Cyclosporin A (CsA) therapy ^[3]
Ganglioside anti-GM2 antibodies	Toluene
Para/post-infectious	Phenytoin
COVID-19	Venlafaxine
HIV infection	Amphetamine use
M.pneumonia	PCP (Phencyclidine)
Cytomegalovirus	Miscellaneous
Scrub typhus	Cerebral venous thrombosis. ^[4]
Human herpesvirus 6	Traumatic brain injury ^[5]
Hepatitis C	Genetic causes; mutation in the potassium channel-related gene, KCTD7. ^[6]
Epstein-Barr virus	
West Nile virus	
Lyme disease	
Psittacosis	
Salmonella	
St Louis encephalitis	
Rickettsia conorii.	

the symptoms characteristic of different DCTD and cannot be definitively classified. These are also known as undifferentiated systemic rheumatic diseases (USRD). The concept of an entity called UCTD was first established in 1980.^[7] Subsequently mixed connective tissue disease (MCTD), and other overlap syndromes were also described.

UCTD is a distinct clinical entity among USRD and its characteristics include: (a) clinical manifestation of at least one of the CTDs, (b) a positive ANA result, and (c) a disease duration of > one year.^[8] Most patients with UCTD are young women who remain in the same category as UCTD throughout their lifetime, although a third can evolved into other well-defined CTDs. Like the DCTD, UCTD is associated with neurological complications such as myositis, inflammatory demyelinating disease, hypertrophic pachymeningitis, and reversible posterior leuko-encephalopathy, among others.^[9] Meningitis, encephalitis, or OF have not yet been described with UCTD.

OF is an abnormal involuntary eye movement that consists of repetitive, irregular, bursts of horizontal saccades without an intersaccadic interval.^[10] It results primarily from an abnormality in the saccadic generation pathway (the saccadic premotor neurons) that consists of the excitatory burst neurons (EBN), inhibitory burst neurons (IBN), and omnipause neurons (OPN). The OPN lies in the paramedian pontine reticular formation. It functions to silence the EBN and IBN in the inter-saccade interval and prevent unwanted movements in between. Increased GABA_A receptor sensitivity in the Olivary-cerebellar-brainstem premotor neuron circuit may also be responsible. Thus, OF occurs when there is mistiming of neuronal activity between the cerebellar nuclei (vermis and fastigial nuclei) and the brainstem premotor neurons.^[11] OF and opsoclonus share a similar pathophysiological mechanism. However, unlike opsoclonus, which can occur in any plane, OF is restricted to the horizontal plane. OF is associated with a wide variety of aetiologies including paraneoplastic syndromes, cerebellar/brainstem encephalitis, metabolic-toxic disturbance, demyelinating disease, viral infections, post-infectious syndrome, or as “isolated OF” when it cannot be attributed to any identifiable cause.^[12] [Table 1] In our case, a transient autoimmune response directed against the OPN neurons due to UCTD, probably caused OF.

Thus, among patients who present with a meningo-encephalitis and OF, a DCTD or a USRD should be in the differential diagnosis. Such patients may respond to IV steroids. Long-term disease-modifying antirheumatic drugs will also need to be considered. Our case adds to the spectrum of neurological involvement in UCTD or USRD.

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Conflicts of interest

There are no conflicts of interest.

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