LETTER TO THE EDITOR

To The Editor

Alien Limb Phenomenon as a Heralding Manifestation of Toxic Leukoencephalopathy

Alien limb phenomenon (ALP) is an intriguing entity characterised by involuntary movements of the limb along with a sense of estrangement. Corticobasal degeneration is the most common cause of ALP followed by other etiologies such as stroke, Creutzfeldt–Jakob disease (CJD).[1,2] Toxin-induced leukoencephalopathy has not been reported as an aetiology of ALP.

We report the case of a 41-year-old gentleman who presented with ALP as a manifestation of toxic leukoencephalopathy caused due to mesalazine.

A 41-year-old right-handed male with history of ulcerative colitis developed an exacerbation of the disease and was managed with steroids and mesalazine. The dosage was hiked up to 2.4 grams from a stable dose of 800 mg/day. After 15 days of increase in the dosage of mesalazine, patient developed difficulty in understanding spoken language along with increasing difficulty in using his right hand. He complained that his hand was not letting him comb his hair or "disturbing" him when he tried to eat an apple with his left hand. He, however, did not report any motor weakness in both the upper limbs and could hold objects equally well with both hands. He also had two episodes of generalised tonic–clonic seizures after which he was brought to the emergency services of our hospital.

On examination, patient was conscious but not responding to verbal command, although on giving painful stimuli he withdrew his upper limb from the painful stimuli. There were no cranial nerve deficits. Motor system examination revealed grade-2 spasticity in all four limbs, bilateral extensor plantar response and generalised hyperreflexia. The most dominant sign was the presence of groping of the right hand by the left hand along with involuntary movements characterised by levitation of both lower limbs and sideways turning of the body (Video 1, Video 2). Patient was not cooperative for detailed neurological examination.

His magnetic resonance imaging (MRI) brain revealed diffusion restriction of periventricular white matter (arrow) along with corpus callosum (Star) in axial diffusion weighted imaging (DWI) (A) and apparent diffusion coefficient (ADC) map (B) (Figure 1). Fluid attenuated inversion recovery (FLAIR) sequences of MRI brain were normal (Figure 1C). Based on imaging and clinical presentation, progressive multifocal leukoencephalopathy, toxic leukoencephalopathy and CJD were kept as differential diagnosis. A repeat MRI scan of the brain demonstrated complete resolution of the diffusion restriction of the white matter changes noted in the previous imaging (Figure 1D, 1E).

On the basis of clinical presentation, temporal relationship with increase in the dosage of mesalazine and resolution of the white matter changes after withdrawing mesalazine, toxic leukoencephalopathy was considered as the most likely diagnosis.

Cerebrospinal fluid (CSF) cytology, biochemistry workup, including CSF protein, sugar and cells, were all within normal range. John Cunningham virus, Herpes simplex virus and Cytomegalovirus polymerase chain reaction and protein 14-3-3 were negative. Electroencephalogram showed diffused generalised slowing and no evidence of periodic discharges. There was no prior history of any illicit drug use, and urine toxic screen was negative for toxins. Complete blood picture, coagulation profile, kidney and liver function tests and metabolic profile were within normal limits.

Mesalazine was stopped after this event. Although the patient had radiological recovery, clinically our patient did not improve as much. He continued to have limb levitations and groping of the right hand. In terms of motor recovery, he started localising a painful stimulus as compared to withdrawal from pain at arrival. He also started having spontaneous eye opening. However, he remained restless and agitated and continued to have ALP. An interval imaging showed generalised cortical atrophy which could explain his lack of clinical improvement (Figure 1F).

Alien hand syndrome was first described in literature over a century ago by Goldstein. It remained an enigma until 1972 when Brion and Jedynak described the *main étrangère*, or what is known as the "strange hand." In 1992, Doody and Jankovic defined alien limb as a feeling that one limb is foreign or "has a will of its own," together with observable involuntary motor activity.[2]

In a case series of ALP, authors reported corticobasal syndrome (CBS) as the most common cause of ALP, followed by stroke. Other uncommon causes included CJD, hereditary diffuse leukoencephalopathy with spheroids, tumour, progressive multifocal leukoencephalopathy, demyelinating disease, progressive dementia not otherwise specified, posterior reversible encephalopathy syndrome (PRES), corpus callosotomy, intracerebral haemorrhage and thalamic dementia.[1]

Toxic leukoencephalopathy can have a myriad of clinical manifestations ranging from inattention, forgetfulness and changes in personality to dementia, coma, and death.[3]

ALP, however, has never been described as a clinical presentation of toxic leukoencephalopathy. A review of literature of cases of ALP by Sarva et al. identified CBS, infarction and CJD as the most common causes of ALP. However, toxic leukoencephalopathy was not a cause in any of the cases.[4]

Three variants of ALP have been described viz. callosal, frontal and posterior or parietal type. Callosal variant is characterised by intermanual conflict, that is, the involved limb opposes the function of the normal limb.[5] Frontal type is due to lesions in supplementary motor area, cingulate cortex and dominant medial prefrontal cortex. Salient features of this type of ALP include impulsive groping, grasping and manipulation of objects.[6] On the other hand, posterior variant is usually caused by lesion in the non-dominant parietal lobe and affects the non-dominant hand.[4]

Patients with posterior ALP have limb levitation, ataxia, non-purposeful or non-conflicting movements and avoidance response, that is, withdrawing hands from stimuli. Other features include cortical sensory deficits, such as astereognosis, graphesthesia, visuospatial defects and neglect.[4]

Our patient had features of all three variants of ALP starting with callosal variant and later on developing levitations of both upper and lower limbs along with groping of the right hand which suggests development of posterior and frontal variants of ALP, respectively.

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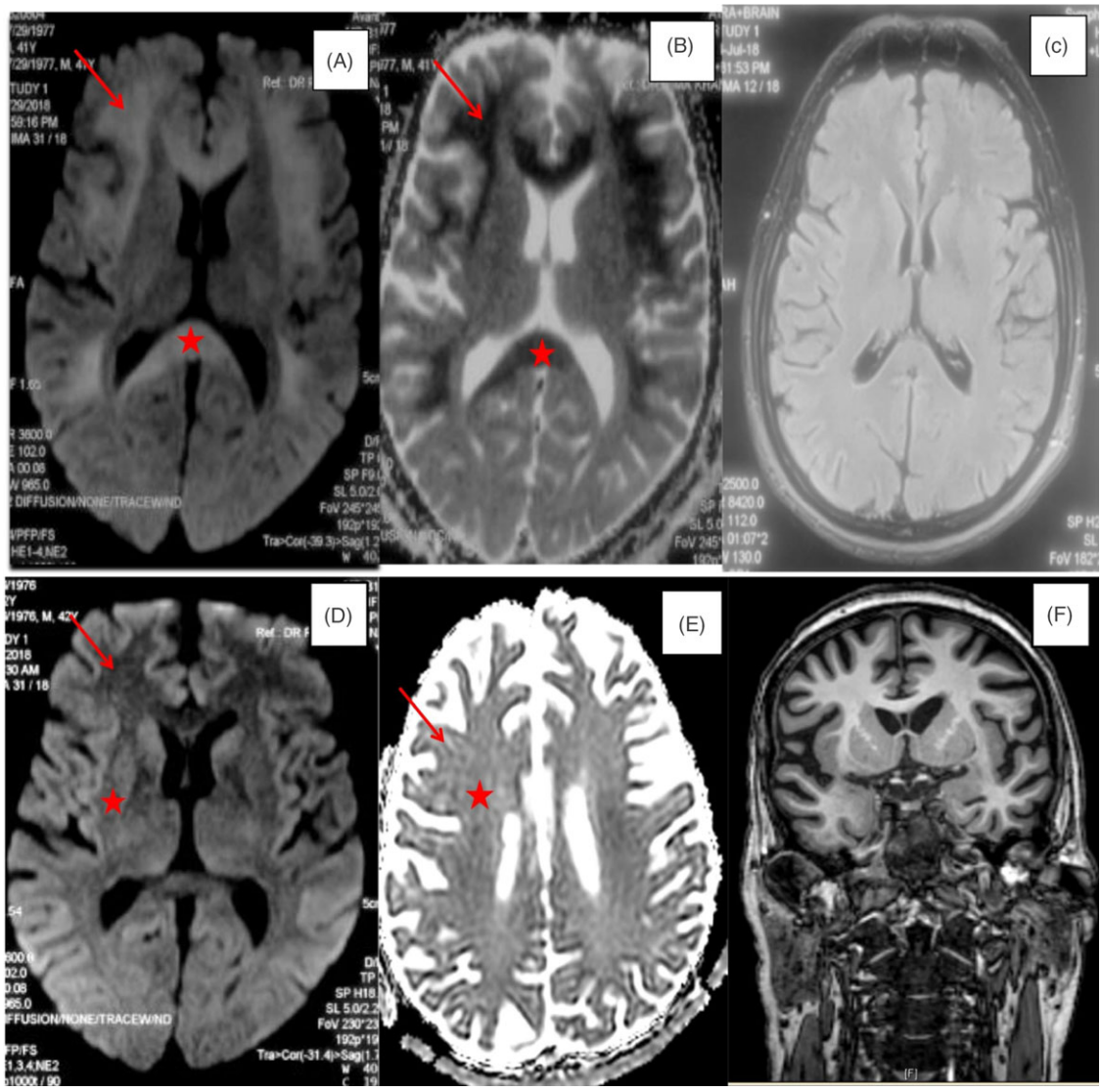

Figure 1: *Axial DWI (A) and ADC map (B) is showing diffusion restriction of periventricular white matter (Arrow). Also note the involvement of corpus callosum (Star). FLAIR is normal (C). Axial DWI(D) at the level of basal ganglia showing resolution of periventricular white matter and corpus callosal signal intensity and diffusion restriction (Arrow). ADC map (E) at the level of centrum semiovale showing mild persistent increased signal intensity (but significantly reduced) in central white matter with patchy diffusion restriction (Star).Coronal T1 (F) showing cortical atrophy in the fronto–parieto–temporal cortices.*

It was also corroborated by neuroimaging, which showed involvement of structures implicated in various forms of ALP.

Our patient's brain MRI scan showed diffusion restriction in the frontal and parietal cortices and corpus callosum which is suggestive of toxic leukoencephalopathy.[7] Lack of any findings on FLAIR and florid diffusion restriction on DWI and ADC makes toxic leukoencephalopathy more plausible instead of PRES, wherein FLAIR hyperintensities, especially in the parieto-occipital cortices, are mostly seen.[7–9] A number of chemotherapeutic agents, drugs of abuse, environmental toxins, antimicrobial agents, radiation therapy, and so on are implicated in toxic leukoencephalopathy. Takahashi et al. and Mut S.E et al. have reported cases of sulfasalazine-induced encephalopathy.[10,11]

In conclusion, ALP is a fascinating neurological phenomenon. The aetiology of ALP continues to broaden. To the best of our knowledge, this is the first case report of ALP being a manifestation of toxic leukoencephalopathy.

Disclosures

PG, DD, RKS, LJDS and MT have no conflicts of interest to declare.

Statement of Authorship

PG created, drafted and edited the manuscript. DD suggested the case for manuscript, created and edited the manuscript. RKS contributed edits to the manuscript. LJDS created the figures and

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contributed edits to the manuscript. MT reviewed and edited the manuscript.

Supplementary Material

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