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Sub-acute onset parkinsonism in an older adult: Dengue encephalitis mimicking as idiopathic Parkinson's disease

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Abstract
Dengue fever is a mosquito-borne arboviral disease caused by dengue virus (DENV) and transmitted by female mosquitoes of the species Aedes aegypti. The prevalence of dengue fever and the spectrum of complications is an ever expanding concern. India being an endemic nation for dengue warrants an early accurate diagnosis, adequate treatment and prompt preventive strategies. Dengue manifesting as a "Neurological illness" is rare and extrapyramidal syndrome including secondary Parkinsonism has been seldom reported. Here, we describe a case of a middle aged lady who presented with features of Parkinsonism following an episode of a brief febrile illness, suggestive of Dengue fever. Dengue was confirmed by a positive serology and Magnetic resonance imaging of brain showed diffuse encephalitis with involvement of substantia nigra and globus pallidus. This case report throws a light on the "unusual" neurological manifestation of dengue infection.

Keywords: parkinsonism, dengue, India, older adult

Introduction
Dengue is an arbo viral infection caused by dengue virus and infection is transmitted by the bite of female Aedes mosquito. This disease is endemic in 120 countries, including India. Recent surveillance data suggests that the clinical manifestations of dengue are dynamic and more neurological complications of dengue are increasingly being reported. The spectrum of neurological manifestations associated with dengue infection include encephalitis, encephalopathy, meningoencephalitis, acute disseminated encephalomyelitis, transverse myelitis, post encephalitis Parkinsonism, myositis, rhabdomyolysis and Guillain Barre Syndrome [1, 2]. Here we report a rare case of Parkinsonism following dengue virus infection in a middle aged woman.

Case Report
A 53-year-old lady presented with sudden onset of slowness in activities of daily living (ADL) since 1 month (October 2019) prior to her hospital admission. Her family members reported that all her symptoms followed a low grade febrile illness that lasted for 1 month. This febrile episode was associated with a headache which worsened with cough. She was treated symptomatically for the above complaints. One month after the febrile illness she was noticed to have become apathetic, keeping to herself and decreased communication with her family members. The change in her personality was contrary to her premorbid socially active personality and thus they sought medical attention for the same. However, there was no history of altered sensorium, behavior abnormality, cognitive decline, seizure or myoclonic jerks. There is no past history of tremors in hands, recurrent falls, and trauma. Her family history for neurological illness was insignificant. Clinical examination at presentation revealed normal hemodynamic parameters. Neurological examination revealed a normal sensorium but apathic with an evidence of facial hypomimia. Her speech was slow and monotonous. Cranial nerve examination revealed bilateral abduction paresis, broken horizontal and vertical saccades, and slow pursuits. She also had bilateral horizontal gaze paresis and flattening of left nasolabial folds. Pupillary examination was normal. Sensory system examination was normal. Motor system examinations showed mild postural tremor in bilateral upper extremities, marked rigidity in all the extremities right more than left and upper limb more than lower limbs. Bradykinesia in all four limbs. Primitive reflexes including Myerson sign, palmo-mental reflex were demonstrable. Deep tendon reflexes were normal and plantar reflexes showed a flexor response. After a thorough clinical examination, a possibility of "secondary Parkinsonism following febrile illness" versus "Mild stage 2 Idiopathic Parkinson's disease (IPD) with rapid worsening following febrile illness" was considered. Investigations done at a center elsewhere during the febrile illness (August 2019) showed hemoglobin-12.47g/dL, total count of 2200cells/cu.mm (relative lymphopenia), platelet count of 92000/cu mm, aspartate transferase- 135 u/L, alanine transferase-50 U/L. Ultrasound scan abdomen showed hepatosplenomegaly. Blood sugar, renal function tests and electrolytes were normal. Dengue virus tests (September/2019) showed negative NS1 antigen test, dengue serology for IgM antibody was positive, whilst IgG was negative. Malaria test was negative. MRI brain showed symmetrical T2 and flair hyper intensities and faint diffusion restrictions [Figure 1] involving bilateral sub cortical frontal, parieto-occipital cerebral white matter fibres, substantia nigra, bilateral thalamus, posterior limb of Internal capsule and cerebellum. Thyroid profile, vitamin B12 levels and EEG were normal. Japanese encephalitis virus serology was negative. Based on positive serology test for dengue virus and diffuse encephalitis on MRI brain, a probable diagnosis of "post encephalitic parkinsonism" was considered. She was started on Levodopa/carbidopa combination (4:1) along with Trihexyphenidyl and topiramate was initiated for residual headache. She made a

partial recovery at 1 month follow up. There was complete recovery in her clinical symptoms at 6 months follow up.

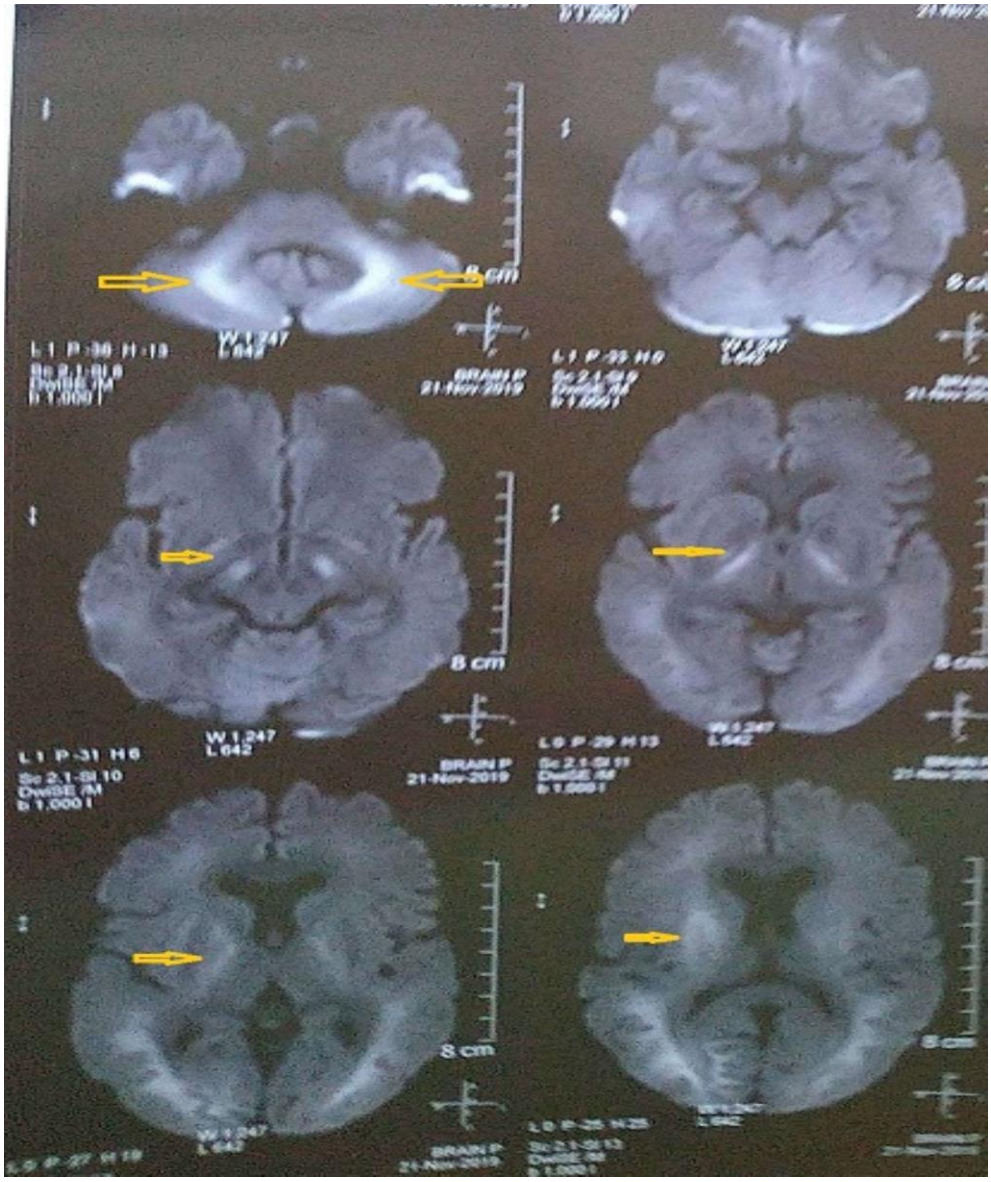

Fig 1: MRI brain showing faint diffusion restrictions involving bilateral sub cortical frontal, parieto-occipital cerebral white matter fibres, substantia nigra, bilateral thalamus, posterior limb of internal capsule and cerebellum.

Discussion

Encephalitis is the most common neurological manifestation following a viral infection and the prevalence varies between 0.5% to 6.2% [2]. Pathogenesis of neurological manifestations of dengue virus infection can be attributed directly to the neurotrophic effect of virus, or to the systemic complication of dengue infection or could be a sequelae of the infection.

Neurological complications have been reported in patients with complicated dengue and rarely observed in uncomplicated dengue fever [3]. Post encephalitic Parkinsonism following dengue infection is an uncommon presentation. Parkinsonism can occur as a result of primary degeneration of dopaminergic neurons as in idiopathic Parkinson's disease or the degeneration could be secondary to various insults *viz.* toxin, viral infection, other neurodegenerative diseases, stroke etc. Clinical features which favored IPD in this case were, age of presentation and predominant upper limb rigidity, whilst MRI abnormality in the form of diffuse encephalitis and an additional positive viral serology for dengue were the pointers towards "secondary parkinsonism" (post dengue encephalitic sequelae).

Other viruses notorious to cause Parkinsonism are influenza, coxsackie, Japanese encephalitis, West Nile, HIV, varicella zoster, Herpes Simplex, Epstein Barr and cytomegalovirus [4]. It has been postulated that these neurovirulent viruses cause death of dopaminergic neurons (striatonigral neurons) by the formation of pathological lewy bodies [5].

Loss of dopaminergic neurons following dengue virus is associated with Parkinsonism, as evident in our case with corroborating imaging evidence, in the form of involvement of substantia nigra. Literature review of neuroimaging findings of dengue encephalitis on MRI scan showed basal ganglia as most commonly affected regions followed by thalamus, temporal lobes, hippocampus and cerebral white matter [6, 7, 8]. Rarely atypical locations such as the brainstem (particularly the substantia nigra), cerebellum and hippocampus have also been reported [9]. Affected regions are usually hyper intense on T2 and FLAIR sequences and demonstrate restricted diffusion in most of the cases. In our case both classical and atypical locations of dengue

encephalitis were observed. Marked Parkinsonism features in our case could be attributed to the involvement of substantia nigra, evidenced as T2 and FLAIR hyper intensities with a restricted diffusion. In IPD though substantia nigra is affected, pathology is at molecular level with subtle MRI findings in the form of loss of normal swallow tail appearance pattern in the substantia nigra on axial susceptibility weighted (SWI) sequence without any hyper intensity on T2 or diffusion restrictions in these region [10]. Other MRI findings in dengue encephalitis reported are dot sign where transient hyper intensities are noted in the splenium of corpus callosum on diffusion, T2 weighted and FLAIR sequences. Patients with neurological manifestations following dengue fever have a good prognosis; however it can be fatal if associated with hemorrhagic fever and shock. Outcome can be unfavorable in cases of extensive parenchymal involvement. Our patient had a near complete recovery despite an extensive parenchymal involvement, as she was promptly diagnosed and was initiated on a short course of drugs against Parkinsonism and remains to be under our thorough surveillance. Her anti-parkinsonism drugs were stopped at one year.

Conclusion

Post Dengue Parkinsonism is a treatable uncommon presentation of Dengue sequelae. High index of suspicion about this complication is warranted amongst the treating clinicians to avoid subjecting the patients to long term anti-Parkinsonism drugs especially in older adults.

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