Am. J. Trop. Med. Hyg., 103(2), 2020, pp. 851–854
doi:10.4269/ajtmh.20-0039

Case Report: Dengue Virus–Triggered Parkinsonism in an Adolescent

Prateek Kumar Panda,[1]† Indar Kumar Sharawat,[1]*† Rishi Bolia,[2] and Yash Shrivastava[2]

[1]*Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, India;* [2]*Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, India*

Abstract. Dengue fever continues to be an important cause of morbidity and mortality in tropical and subtropical countries. A wide range of neurological manifestations including dengue encephalopathy, Guillain–Barre syndrome, acute disseminated encephalomyelitis, transverse myelitis, cranial nerve palsies, and myositis have been reported following dengue infection. But parkinsonism secondary to dengue virus infection is uncommon, with only three published case reports in adults and one in children. We describe a 13-year-old pre-morbidly normal boy, who presented with bradykinesia, bradyphonia, mask-like facies, and cogwheel rigidity while recovering from uncomplicated DF. He responded favorably to levodopa/carbidopa supplementation and had resolution of symptoms over the next 2 weeks. We also did a comparative review of all published cases of dengue-induced parkinsonism. Post-dengue, parkinsonism is uncommon, and treating clinicians should be aware of this uncommon but treatable neurological complication of a common arboviral infection.

INTRODUCTION

Dengue fever (DF) continues to be an important cause of morbidity and mortality in tropical and subtropical countries.[1] A wide range of neurological manifestations has been reported following dengue infection.[2] These include dengue encephalopathy, Guillain–Barre syndrome, acute disseminated encephalomyelitis, transverse myelitis, cranial nerve palsies, and myositis.[2] As such, neurological complications of dengue infection are quite uncommon. Furthermore, parkinsonism secondary to dengue virus infection is uncommon, with only three published case reports in adults and one in children.[3–5] We describe a 13-year-old, pre-morbidly normal boy, who developed Parkinsonism after dengue infection. We also did a comparative review of all published cases of dengue-induced parkinsonism in children and adults.

CASE REPORT

Clinical presentation. A 13-year-old boy, resident of the northern part of India, presented with fever for the past 2 days. The fever was acute onset, high grade (up to 104° F), was associated with chill and rigor, severe malaise, body ache, and erythematous, non-blanching, and nonpruritic rashes over the face and trunk. On laboratory evaluation, he had normal hemoglobin (15.1 gm/dL), decreased total leukocyte count (2,950/uL), and thrombocytopenia (platelet count-87,000/uL). Because DF was the most common cause of viral illness with thrombocytopenia in the region, the NS1 antigen was tested, and it was found to be positive. Remaining all laboratory investigations were normal. The child did not develop any warning signs, and the fever resolved after 3 days of admission. However, on day 6 of illness, he developed bradyphonia, unclear speech, and gait instability. He also had bradykinesia while trying to perform any purposeful activity like getting up from the bed. Moreover, the next day onward, he developed increased stiffness, more in the legs than in the arms, mainly in the form of cogwheel rigidity. He also had mask-like facies and stooped posture while walking. However, he did not have any change in sensorium, focal deficit, behavioral abnormality, resting tremor, or diurnal variation in his symptoms.

Diagnostic evaluation. Magnetic resonance imaging (MRI) of the brain (Figure 1), cerebrospinal fluid (CSF) examination, and electroencephalography were within normal limits. Workup for systemic lupus erythematosus, autoimmune encephalitis, anti-basal ganglia encephalitis, Wilson disease, and other neurometabolic diseases were also noncontributory. The diagnosis of dengue-induced parkinsonism was considered taking into account the clinical and laboratory parameters.

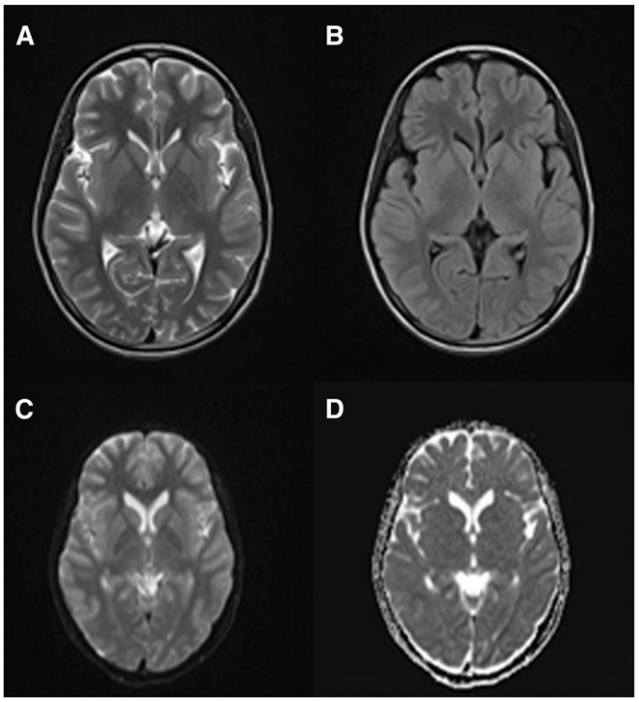

FIGURE 1. Magnetic resonance imaging of the brain of a child with dengue-triggered parkinsonism. T-weighted (**A**), fluid-attenuated inversion recovery (**B**), diffusion-weighted (**C**) sequences, and apparent diffusion coefficient map (**D**) does not show any basal ganglia or parenchymal abnormalities.

*Address correspondence to Indar Kumar Sharawat, Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh 249203, India. E-mail: sherawatdrindar@gmail.com
† These authors contributed equally to this work.

Management and follow-up. Oral levodopa–carbidopa combination at an escalating dose of 100–200 mg/day in divided doses was administered, and the boy showed a favorable response, with gradual resolution of symptoms over the next 2 weeks. On a regular follow-up at three months, he did not have any abnormality in gait or speech, and his neurological examination was essentially normal.

DISCUSSION

Dengue fever is an arboviral illness caused by any of the four dengue virus serotypes DENV 1–4. Its primary mode of transmission between humans is by the female *Aedes* mosquito. The disease is most prevalent in tropical and subtropical regions of the world. Infection with dengue virus may result in symptoms of varying severity, ranging from mild asymptomatic DF to severe DF, with warning signs and potentially life-threatening dengue hemorrhagic fever and dengue shock syndrome.[1]

Neurological complications of dengue are relatively uncommon. Meningoencephalitis, acute disseminated encephalomyelitis, transverse myelitis, ischemic and hemorrhagic strokes, cerebellar syndrome, myositis, peripheral neuritis, Guillain–Barre Syndrome, and optic neuritis have all been reported in various case reports and series from various parts of the world. However, acute onset parkinsonian features triggered by dengue viral infection have uncommonly been reported.[3]

Viruses known to induce parkinsonism or related symptoms include Japanese encephalitis virus, West Nile virus, coxsackie virus, human immunodeficiency virus (HIV), varicella-zoster virus, herpes simplex virus (HSV), Epstein–Barr virus, and cytomegalovirus.[6] Exact pathophysiology behind any post-viral parkinsonism is yet to be elucidated. Efforts to detect viral particles in the brain or antibodies in the serum or the CSF have been mostly unsuccessful.[6] Three different pathophysiological processes such as a direct neurotropic invasion, systemic complication, and postinfectious autoimmune phenomenon have been implicated in these complications.[6] Recent immunohistochemical work in post-viral parkinsonism favors the role of complement proteins and interferons in post-viral encephalitis.[6]

A review of the published literature in "Pubmed," "Google Scholar," and other electronic databases revealed only four cases of parkinsonism triggered by dengue viral infection till now. Among these four cases, only one case reported by Fong et al.[4] was in the pediatric age-group. A comparison of clinical features of all five cases, including the index case, has been shown in Tables 1 and 2. Interestingly, all affected cases are male, and in all cases, CSF examination was normal. Dengue virus was not isolated by polymerase chain reaction (PCR) in the CSF of any of these cases during parkinsonism. Magnetic resonance imaging brain was also normal in three of four previously reported cases, and only one case showed microinfarcts in basal ganglia.

Most of them had dengue IgG positivity, indicating a history of previous dengue infection too.[3,4] This is not surprising, as it has been demonstrated that neurological manifestations of

TABLE 1
Comparison of clinical and laboratory parameters in the initial phase of illness (dengue fever)

Variable	Azmin et al. (2013)	Fong et al. (2014)	Bopethha et al. (2017)	Manappallil et al. (2019)	Index case
Age (years)	18	6	69	48	13
Gender	Male	Male	Male	Male	Male
Premorbid illness	Nil	Nil	Non–Hodgkin lymphoma 4 years back (treatment completed)	Nil	Nil
Clinical features suggestive of dengue	Fever, myalgia, lethargy, headache, and gum bleeding	Fever and lethargy	Fever, myalgia, headache, joint pain, and anorexia	Fever and myalgia	Fever, myalgia, rash, and joint pain
Duration of dengue fever (days)	6	8	8	5	5
Complications	Nil	Nil	Nil	Microinfarcts in basal ganglia	Nil
Hemoglobin (gm/dL)	15.8	NA	10.2	18	15.1
Total leukocyte count	3,000/uL	3,700/uL	5,590/uL	2,500/uL	2,950/uL
Total platelet count	64,000/uL	176,000/uL	100,000/uL	15,000/uL	87,000/uL
Alanine transaminase (IU/mL)	170	Normal	55	224	53
Serum creatinine (mg/dL)	1.0	Normal	1.0	Normal	0.6
Serum electrolytes	Normal	Normal	Normal	Normal	Normal
NS1 antigen	Positive	Positive	Negative	Positive	Positive
Dengue IgM	Negative	Positive	Positive	Positive	Negative
Coinfection	Nil	Nil	Nil	Nil	Nil
Drugs	Not specified	Intravenous normal saline	Intravenous normal saline	Intravenous normal saline, paracetamol, folic acid supplements, and pantoprazole	Intravenous normal saline and oral paracetamol
Blood products	Nil	Nil	Nil	Nil	Nil

TABLE 2
Comparison of clinical and laboratory parameters in the later phase of illness (dengue-induced parkinsonism)

Variable	Azmin et al. (2013)	Fong et al. (2014)	Bopethha et al. (2017)	Manappallil et al. (2019)	Index case
Onset of neurological symptoms	Day 6 of illness	Day 9 of illness	Day 8 of illness	Day 4 of illness	Day 6 of illness
Features suggestive of parkinsonism	Bradykinesia, bradyphonia, and broad-based ataxic gait	Bradykinesia and akinetic mutism	Bradykinesia, bradyphonia, stooped posture, broad-based gait, expressionless facies, and cogwheel rigidity	Cogwheel rigidity, bradykinesia, and resting tremor	Bradykinesia, bradyphonia, shuffling gait, mask-like facies, and cogwheel rigidity
Other neurological signs and symptoms	Cerebellar ataxia, right brachial plexopathy, and cranial neuropathy (11, 12 CN on the right side)	Encephalopathy and intermittent dystonia	Nil	Delirium and mutism	Nil
Gadolinium-enhanced magnetic resonance imaging brain findings	Normal	Normal	Normal	Microinfarcts in basal ganglia	Normal
CSF examination	Acellular, protein-55 mg/dL and sugar-45 mg/dL (blood sugar-97 mg/dL)	Normal	45 cells/ul (92% lymphocytes), rest normal	3 cells/uL, protein-35 mg/dL, and glucose 60 mg/dL	Acellular, protein-34 mg/dL, and sugar-63 mg/dL (blood sugar-87 mg/dL)
EEG	Not done	Diffuse delta slowing	Evidence of encephalitis	Not done	Normal
Nerve conduction study	Unremarkable	Not done	Not done	Not done	Unremarkable
Electromyography	Chronic denervation changes in the right deltoid and the right trapezius suggestive of right brachial plexopathy	Not done	Not done	Not done	Unremarkable
ANA	Negative	Not done	Negative	Not done	Negative
HIV	Negative	Not done	Negative	Negative	Negative
Neurometabolic screen	Not done	Not done	Not done	Not done	Negative
Serum ceruloplasmin	Not done	Not done	Not done	Not done	Normal
CSF autoimmune encephalitis antibody profile	Not done	Not done	Not done	Not done	Negative
Serum anti-dopamine receptor 2 antibody	Not done	Not done	Not done	Not done	Negative
Repeat serum/CSF dengue IgM	Positive	Not done	Positive	Not done	Positive
CSF neurotropic virus PCR	Negative	Not done	Negative	Not done	Negative
Levodopa + carbidopa	–	No response to the 5-day course	400 mg/day	100 mg/day	200 mg/day
Corticosteroid	Methylprednisolone 500 mg OD for 3 days	Methylprednisolone pulse followed by intravenous dexamethasone	–	Dexamethasone 8 mg q6-hourly for 5 days	–
Clinical improvement	1 month	7 weeks	1 month	2 weeks	2 weeks
Residual symptoms	Weakness of right deltoid and right infraspinatus	Nil	Nil	Nil	Nil

CSF = cerebrospinal fluid.

dengue infection are more prevalent in cases with secondary dengue infection. Non-neutralizing antibody-mediated or antibody-dependent enhancement is responsible for increased severity in secondary dengue infection.[2] Recently, autoimmune encephalitis has been reported during the recovery from viral encephalitis, especially HSV encephalitis, causing secondary worsening like our case.[7] Post-viral autoimmune herpes simplex encephalitis is sometimes associated with autoantibodies to N-methyl-D-aspartate receptor or dopamine-2 receptor.[8] Often it also presents with predominant movement disorders like chorea or dyskinesia.[7]

Of the four cases in the existing literature, three had a favorable response with intravenous corticosteroids.[3–5,9] Although most of the previously reported cases have not been investigated extensively to rule out the possibility of autoimmune etiology, however, clinical features of all these cases resemble that of autoimmune encephalitis. So, a possibility of seronegative autoimmune encephalitis, presenting with predominant parkinsonian features, cannot be ruled out completely. Even the pathophysiology behind dengue encephalitis, or more aptly called dengue encephalopathy, also includes autoimmune phenomenon, apart from vasculopathy, dyselectrolytemia, and direct neurotrophic effect.[1] Dengue encephalopathy usually occurs during the acute stage. Acute risk factors, such as prolonged shock, hypoxia, systemic or cerebral hemorrhages, and metabolic disturbances, usually predispose this entity.[1]

Cerebrospinal fluid analysis usually remains normal. Direct vascular damage to basal ganglia was only present in one of the four previous cases, leading to microinfarcts. All these findings together suggest that dengue-induced parkinsonism is an entity distinguished from dengue encephalopathy, which invariably occurs after the recovery of acute illness.

As described earlier, the existing literature suggests the role of both levodopa and corticosteroids in post-dengue parkinsonism.[3–5,9] But in our case, corticosteroids were not needed, as there was a favorable response to levodopa. Irrespective of the treatment modality used, parkinsonian features usually subsided within 2–7 weeks of the onset, and one of the four cases had residual sequelae due to other associated neurological complications.[3–5,9]

CONCLUSION

The aforementioned report and literature review intend to be aware of the clinicians regarding parkinsonism as an uncommon neurological complication of such a common arboviral infection such as DF. Especially in endemic countries, it is imperative to consider this cause in a child with acute onset parkinsonism. It is uncommon, yet completely treatable. Levodopa and corticosteroids are available therapeutic options for this entity.

Received January 16, 2020. Accepted for publication April 7, 2020.

Published online May 4, 2020.

Acknowledgment: The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

Disclosure: We confirm that we have read the *Journal*'s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' addresses: Prateek Kumar Panda and Indar Kumar Sharawat, Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, India, E-mails: drprateekpanda@gmail.com and sherawatdrindar@gmail.com. Rishi Bolia and Yash Shrivastava, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, India, E-mails: rishibolia@yahoo.co.in and dr.yash.2409@gmail.com.

REFERENCES

1. Li GH, Ning ZJ, Liu YM, Li XH, 2017. Neurological manifestations of dengue infection. *Front Cell Infect Microbiol 7:* 449.
2. Murthy JMK, 2010. Neurological complications of dengue infection. *Neurol India 58:* 581–584.
3. Azmin S, Sahathevan R, Suehazlyn Z, Law ZK, Rabani R, Nafisah WY, Tan HJ, Norlinah MI, 2013. Post-dengue parkinsonism. *BMC Infect Dis 13:* 179–182.
4. Fong CY, Hlaing CS, Tay CG, Ong LC, 2014. Post-dengue encephalopathy and parkinsonism. *Pediatr Infect Dis J 33:* 1092–1094.
5. Bopeththa BVKM, Ralapanawa U, 2017. Post encephalitic parkinsonism following dengue viral infection. *BMC Res Notes 10:* 655–658.
6. Jang H, Boltz DA, Webster RG, Smeyne RJ, 2009. Viral parkinsonism. *Biochim Biophys Acta 1792:* 714–721.
7. Leypoldt F et al., 2013. Herpes simplex virus–1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology 81:* 1637–1639.
8. Chaudhary H, Kasinathan A, Sharawat IK, Saini AG, Mahadevan A, Sankhyan N, 2018. Post-herpetic autoimmune encephalitis. *Indian J Pediatr 85:* 691–692.
9. Manappallil RG, 2019. Parkinsonism following basal ganglia infarction in Dengue fever. *Asian J Med Sci 10:* 62–64.