Rivaroxaban: A Possible Cause of Guillain–Barre Syndrome

Sir,

Guillain–Barre syndrome (GBS) is the most common cause of acute flaccid paraparesis or quadriparesis after eradication of polio with an incidence of 1–2 cases per 100,000 per year throughout the world.[1] Nerve conduction studies (NCSs), cerebrospinal fluid (CSF) analysis, and magnetic resonance imaging (MRI) add supportive evidence for the diagnosis. In the early stages, clinical evidence is diagnostic whereas electrophysiological studies may be normal or may have only absent H reflex throughout the course.[2] Recent infections and vaccinations are the most common triggers whereas pregnancy and parturition, bariatric surgery, renal transplantation, and trauma are also reported.

Drug-induced GBS is a rare entity and considered infrequent. It was first observed in a group of people who received the influenza vaccine.[3] Most common drugs reported so far are allopurinol, gold therapy, d-penicillamine, streptokinase, corticosteroids, captopril, oxytocin, zimeldine, gangliosides, danazol, tumor necrosis factor-alpha antagonists, and second-generation antipsychotics such as risperidone.[4-6] Fluoroquinolones and penicillin were more common antibiotics reported with the occurrence of GBS. Among thrombolytics, streptokinase causing GBS has been reported so far.[7] Newer anticoagulants such as rivaroxaban, apixaban, and dabigatran have risen to limelight in the current era of oral anticoagulation. The onset of GBS symptoms after initiation of the drug was noted as few as 6 days to 14 months.

We had a 55-year-old diabetic male who presented with an acute-onset ascending quadriparesis with numbness and paresthesia over toes and fingertips for 10 days. The symptoms initially started with distal paresthesia in lower limbs and then buckling of knees with minor difficulty in walking. Over the next 5 days, he needed two-person support along with hand grip weakness. His cranial nerves were normal. He had no prior history of fever, diarrhea, vomiting, upper respiratory tract illness, trauma, or any recent vaccination. He recently got admitted with acute-onset headache with intermittent right hemianesthesia and dysarthria. He had absent ankle jerks with well-preserved other deep tendon reflexes. His MRI brain plain and contrast with venogram showed evidence of cerebral venous thrombosis. He had desaturation and persistent oxygen requirements during the hospital stay. In suspicion of pulmonary thromboembolism, contrast-enhanced computed tomography thorax was done and confirmed the presence of pulmonary thromboembolism. Prothrombotic work up (serum fasting homocysteine; antiphospholipid antibody; protein C and protein S) done was negative. He was started on rivaroxaban on April 3, 2018, and got discharged after 10 days of hospital stay. He was able to walk independently without support, with no limb weakness and no dyspnea and maintaining normal room air saturation of 97%. He then developed acute-onset ascending quadriparesis after 5 days of discharge, i.e., on April 8, 2018. Clinically, he was conscious, alert, and well oriented with normal vitals (blood pressure of 130/80 mmHg and pulse rate of 68 beats/min). His higher mental functions and cranial nerve examination were normal. He had hypotonia in lower limbs. His upper limb power was 3/5 with bilateral hand grip being weak and lower limbs weakness (power of distal – 3/5 and proximal – 2/5) with truncal weakness, but the neck power was normal. He had generalized areflexia with glove and stocking type of sensory loss up to the knee.

His routine biochemistry and hemogram were normal, but elevated glycosylated hemoglobin (10.4%). Serology for hepatitis viruses, human immunodeficiency virus, syphilis, and the autoimmune workup [ANA IF (antinuclear antibody - immunofluorescence, ANCA (anti-neutrophilic cytoplasmic antibodies) profile, complement) tested were normal. CSF analysis at 2 weeks was done and showed (cells – 3 cells/cu. mm, protein – 51 mg/dl, and sugar – 59 mg/dl) levels with no features suggestive of infection. MRI whole spine with brain was normal.

NCSs showed normal distal latencies with normal compound motor action potential amplitudes distally with conduction block with more than 50% reduction in amplitude on proximal stimulation in both tibial and right peroneal nerves. F-wave latencies were prolonged in left peroneal and tibial nerves. Sensory nerve conductions showed reduced sensory nerve action potential (SNAP) in the right ulnar nerve with normal peak latency and conduction velocity, with both sural nerves being non-recordable. NCS was suggestive of a demyelinating polyneuropathy. Both clinically and electrophysiologically, there was substantial evidence of demyelinating neuropathy. Repeat NCS done after 1 month (May 17, 2018) [Table 1] showed prolonged distal latencies in the right tibial and peroneal nerves with normal amplitudes distally and conduction block with more than 50% reduction in amplitude on proximal stimulation in both tibial and right peroneal nerves with reduced conduction velocities. The rest of the tested nerves are within normal limits. F-wave latencies are prolonged in bilateral tibial and left peroneal nerves, with absent F-wave latency in the right peroneal nerve. Sensory nerve conductions in repeat NCS was showed reduced SNAP in the right sural nerve with normal peak latency and conduction velocity with left sural nerve and right ulnar SNAPs being non-recordable. As there was no prior infection or vaccination, further probation has done for the etiology of GBS. We reviewed his drug chart, and rivaroxaban was considered as the most probable cause of GBS in his case. The drug was stopped and changed to conventional oral anticoagulant acenocoumarin for the underlying prothrombotic state. He was treated with intravenous immunoglobulin (0.4 mg/kg/day for 5 days) along with neurorehabilitation, following which he improved and was able to walk without support within 2 months of stoppage of medication.

Table 1: Nerve conduction studies values

	NCS 19.4.2018			NCS 17.5.2018		
Motor Nerve conduction study						
Nerve	**Latency (ms)**	**Amplitude (mV)**	**CV (m/s)**	**Latency (ms)**	**Amplitude (mV)**	**CV (m/s)**
Left median						
Wrist	3.4	14.7	51.8	3.3	18.3	52.1
Elbow	8.4	13.5		8.3	16.5	
Right median						
Wrist	3.6	15.3	50.4	3.4	14.3	52.7
Elbow	8.8	14.7		8.4	13.3	
Left Ulnar						
Wrist	2.6	14.6	50.4	2.7	15.6	53.8
Below elbow	7.8	13.8		7.6	14.7	
Right ulnar						
Wrist	2.5	15.5	50	2.8	10.8	50.4
Below Elbow	8	15.5		8.2	9.7	
Left peroneal						
Ankle	4.2	7	41.4	3.6	5.2	41.3
Head of fibula	14.2	5.3		13.6	3.5	
Right peroneal						
Ankle	4.3	3.6	33.3	4.8	1	38
Head of fibula	16.2	1.7		15.5	0.3	
Left tibial						
Ankle	3.9	15.1	33.5	3.8	12	32.9
Popliteal fossa	16.6	6.9		16.8	4.9	
Right tibial						
Ankle	4.4	10.4	33.9	5.2	9.5	35.6
Popliteal fossa	16.6	5.1		16.8	3	
F waves	**Latency (ms)**			**Latency (ms)**		
Left median	31.4			34		
Right median	32.4			33.1		
Left ulnar	22			35.1		
Right ulnar	33.9			33.5		
Left peroneal	63.1			65.7		
Right peroneal	53.8			NR		
Left tibial	61.7			68.8		
Right tibial	56.3			69.2		
Sensory nerve conduction study						
Sensory nerves	**Peak Latency**	**Amplitude**	**CV**	**Peak Latency**	**Amplitude**	**CV**
Right median	2.9	36.1	53.5	2.7	16.2	57.4
Left median	2.9	11.9	54.9	2.8	18.1	55.8
Right ulnar	2.4	1.5	50.4	NR	NR	NR
Left ulnar	2.2	26.3	58.3	2.3	14.2	56.1
Right sural	NR	NR	NR	2.1	0.7	68.4
Left sural	NR	NR	NR	NR	NR	NR

CV=Conduction velocity, NCS=Nerve conduction study, NR=Not recordable, mV=millivolts, m/s=metres/second

Rivaroxaban is a direct factor Xa inhibitor, which interferes with thrombin formation and effectively interrupts the coagulation cascade. GBS is considered as one of the side effects seen in about 0.01% of patients on rivaroxaban. GBS occurs within 1 month of intake of the drug. The cause–effect relation is usually unknown – probable pathogenesis considered was an immune allergic reaction to the drug or likely direct neurotoxic effect of the drug over myelin secondary to molecular mimicry causing demyelination. The clinical picture and treatment of drug-induced GBS are like that of postinfectious GBS.[8] Ideally stopping the offending drug is the crucial step in the line of management. In this case, rivaroxaban was considered as a possible etiology of GBS. Although direct correlation cannot be proven in this case, the history, timing and nature of clinical events, and their improvement after cessation of drug and IVIg strongly favor drug-induced GBS. Only one food and drug administration (FDA) report has been reported so far regarding the association of rivaroxaban and GBS.[9] Hence, we want to

highlight the same. Detailed drug history is always to be probed for etiology. Drug-induced GBS must be kept into consideration in the association, apart from infections and vaccination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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