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REVIEW

Beyond thrombocytopaenia, haemorrhage and shock: the expanded dengue syndrome

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ABSTRACT
Dengue infection classically presents with fever, thrombocytopaenia, and varying degrees of plasma leakage, giving rise to shock. However, a myriad of other manifestations, involving the cardiovascular system, the nervous system, the liver, the kidneys, the gut and the haematological system have been reported in dengue. This review summarizes these varied presentations.

KEYWORDS
Dengue; expanded dengue syndrome; atypical; unusual; myocarditis; encephalitis

Background

Dengue is caused by a flavivirus transmitted by *Aedes* mosquitoes. It is prevalent in tropical and subtropical countries, and is currently endemic in South East Asia and the Asia-Pacific Regions. Almost 4 billion people are at risk, and 50–100 million people are infected with dengue each year [1,2]. There are four serotypes of dengue virus, DEN 1–4. Dengue infection has varied presentations, ranging from undifferentiated fever to life threatening haemorrhagic fever (DHF), characterised by plasma leakage and shock syndrome (DSS). Dengue must be considered as a probable diagnosis in patients who live in or recently travelled to a dengue endemic area, presenting with fever and at least two of the following: nausea, vomiting, rash, aches and pains, positive tourniquet test, leukopaenia, or any of a set of defined warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, hepatomegaly, increase in haematocrit with rapid decrease in platelet count). The latter warning signs may herald the onset of severe dengue, characterised by severe plasma leakage resulting in shock and other manifestations of third space fluid accumulation, and severe bleeding [3].

The classical presentation in dengue is fever with sharply dropping platelet counts, which may or may not be associated with plasma leakage, the latter resulting in either compensated or uncompensated shock. The shock syndrome can result in multi-organ failure and death. Apart from the classical presentation, dengue infection can result in a myriad of unusual clinical manifestations, which are grouped under the title 'expanded dengue syndrome'. This group generally includes specific organ involvement, with atypical presenting features. In this paper, we describe unusual or atypical manifestations of dengue infection, based on a review of the literature.

Methods

We performed a PUBMED search for all papers published in English language using the keywords 'dengue', AND 'atypical' OR 'rare' OR 'unusual' in title and abstract. There were 4912 abstracts in the original search with duplicates removed. The software Thomson – Reuters Endnote X7 was used to filter articles. All abstracts were read through independently by the authors. Observational studies, clinical trials, case series, and case reports of patients with a confirmed diagnosis of dengue were screened for inclusion. We also searched the bibliography of review papers on dengue for reports of unusual or atypical manifestations of dengue. We included papers which provided data regarding atypical manifestations of dengue. In all included reports, a laboratory diagnosis of dengue was considered essential, by any of the established diagnostic tests (positive dengue IgM ELISA, positive dengue NS1 antigen, positive dengue PCR). We excluded reports where co-infection with other diseases were present. Data from a total of 172 papers are reviewed here.

Results

The diverse manifestations of dengue are categorised below according to the primary organ system involved. Data from observational studies were used to estimate the frequency of occurrence of certain manifestations. For many manifestations, data was only available from

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case reports, and it was not possible to estimate the frequency of occurrence (Table 1).

Cardiac manifestations

A variety of cardiac manifestations have been reported in dengue infection. The true incidence of cardiac involvement is difficult to gauge, as different studies define different parameters as evidence of cardiac involvement [4–6]. Cardiac involvement of varying degrees have been described, ranging from arrhythmias (which are commonly seen), to myocardial depression and myocarditis.

Electrocardiographic abnormalities

ECG changes are the most commonly described cardiac manifestations. The patterns of certain ECG changes have been described in several observational studies from Sri Lanka and India [6–8], as well as in several case reports. Sinus bradycardia has been noted as the predominant arrhythmia, in several descriptive studies [6–8]. Other abnormal rhythms reported were sinus tachycardia [6,8], 2nd degree heart block [7,9], complete heart block [10–12], sino-atrial block [13], ventricular bigeminy and trigeminy [8,14], paroxysmal SVT [15], and acute atrial fibrillation [16,17]. Almost all reported arrhythmias were transient, with complete recovery on discharge. In a prospective study done in Sri Lanka during a dengue epidemic in 2005, 62.5% of ECG abnormalities were documented in patients with uncomplicated dengue fever, suggesting that ECG abnormalities are not related to the severity of dengue. In this study, although 80% of patients had hypotension, only two were diagnosed to have myocarditis [18]. ECG abnormalities are thought to be more common among patients with secondary dengue infection [6]. Another descriptive study done among children, with 18–24 hour Holter monitoring during the convalescent phase, did not demonstrate an association between the clinical severity of dengue and arrhythmias [19]. None of the observational studies gave details on comorbidities which may increase the likelihood of arrhythmias [6–8], while some specifically excluded patients with pre-existing heart disease [7]. It is noteworthy that arrhythmias may occur due to deranged metabolic states and electrolyte imbalance in severe dengue with organ dysfunction. In one observational study of non-severe dengue patients, the presence of ST-T changes or bundle branch block appeared to increase the risk of developing hypotension and tachy-brady arrhythmias; this study specifically excluded patients with abnormal electrolytes or renal dysfunction [6], thus suggesting that arrhythmias may be independent of electrolyte disturbance.

Echocardiographic changes

Transient myocardial depression has been described among children as well as adults in several prospective studies in Asia [5,20–22]. This phenomenon has been observed mainly during the toxic phase. The frequency of reduced ejection fraction was significantly higher in dengue shock syndrome and dengue haemorrhagic fever than dengue fever [21]. Mild to moderate reduction in ejection fraction has been detected by echocardiography as well as more specific radionuclide ventriculography, with mean values of 47.06% and 41.69%, respectively [22]. This myocardial depression is a attributed to a functional impairment, as 99m Tc pyrophosphate imaging did not show myocardial necrosis [22]. In an observational study among children, it was noted that patients with low ejection fraction required more aggressive fluid replacement, and low ejection fraction was associated with larger pleural effusions and respiratory embarrassment [23]. Apart from ejection fraction, end diastolic volume and cardiac index were found to be low. In addition, reduced systolic myocardial septal velocities and right ventricular systolic and diastolic velocities have been detected, in a study done in Vietnamese children [21].

Myocarditis/pericarditis

The prevalence of myocarditis in dengue infection ranges from 9% to 15% [24–26]. A prospective study carried out in China during an outbreak has shown that the prognosis of dengue patients with or without myocarditis did not differ [26]. However, there have been several case reports which have reported fatal outcomes in patients with dengue myocarditis [24,27–31]. A significant positive association between myocarditis and the severity of dengue has been shown in one study [26]. Autopsy findings have shown viral particles in cardiac muscle, by immunohistochemistry, suggesting a possible cardiotropism of the dengue virus [24,32].

Pericarditis has been known to occur [33], and there is one report of severe pericardial effusion with cardiac tamponade requiring pericardiocentesis in early dengue infection [34]. This could be a result of the plasma leakage syndrome.

There is insufficient data to determine whether cardiac involvement is more common in severe dengue. Many case reports showing significant cardiac involvement are of patients with severe forms of dengue. The evidence from observational studies is less clear. One study showed that those with warning signs of severe dengue were more likely to develop cardiac involvement [8], another study showed no difference [7], while the third was not designed to demonstrate such a correlation [6].

Neurological manifestations

Nervous system involvement is less common in dengue, with a reported incidence of 0.5–5.4% [35–40]. Encephalopathy is the most common presentation [37,39,41–44], and is an important cause of death in dengue [39]. It occurs mostly in the presence of organ

Table 1. Summary of studies providing data on atypical manifestations of dengue.

Manifestations	Frequency	Observational studies	Case series/case reports
CARDIAC			
Sinus Bradycardia	8.77–32%	Kularatne et al [6], Arora et al. [7], Sheetal et al. [8]	-
Sinus Tachycardia	3.51%	Kularatne et al. [6], Sheetal et al. [8], La-Orkhun et al. [19]	-
Atrioventricular block	0.03%	Arora et al. [7], Sheetal et al. [8], Neeraja et al. [25], Li et al. [26], Miranda et al. [32]	Nigam et al. [9],Navinan et al. [10], Virk et al. [11], Dhariwal et al. [12]
Sino-atrial exit block	NA	-	Kaushik et al. [13]
Ventricular bigeminy and trigeminy	1%	Sheetal et al. [8]	Matthias et al. [14]
Paroxysmal SVT	NA	Pothapregada et al. [152]	-
Acute atrial fibrillation	NA	-	Mahmod et al. [16], Horta Veloso et al. [17]
Myocarditis or myocardial depression on echocardiography	9–15%	Khongphatthanayothin et al. [5], Kirawittaya et al. [20], Yacoub et al. [21], Wali et al. [22], Neeraja et al. [25], Li et al. [26]	Miranda et al. [24], Marques et al. [27], Tahir et al. [28], Sane et al. [29], Ku et al. [30], Lee et al. [31]
Pericarditis/effusion	NA	-	Tayeb et al. [33], Bendwal et al. [34]
NEUROLOGICAL			
Encephalitis, encephalopathy, meningitis	0.2–52%	Solomon et al. [36], Misra et al. [40], Laul et al. [41], Pancharoen et al. [42], Sil et al. [43], IKumar et al. [44], Cam et al. [45]	Aggarwal et al. [37], Muzzafar et al. [46], Goswami et al. [47]
Intracranial haemorrhage	0.04–0.1%	Koshy et al. [35], Kumar et al. [49]	Ahamed et al. [38], Bharti et al. [51], Jayasinghe et al. [48], Sam et al. [50]
Transverse myelitis	0.28–5%	Weeratunga et al. [60], Sil et al. [43], Misra et al. [39]	Mota et al. [52], Chanthamat et al. [53], de Sousa [54], Fong et al., Larik et al. [55], Mo et al. [56], Patras et al. [57], Seet et al. [58], Tomar et al. [59]
ADEM	0.09–5%	Koshy et al. [35], Sil et al. [43], Kamath et al. [70]	Gupta et al. [62], Brito et al. [63], Karoli et al. [65], Fragoso et al. [64], Viswanathan et al. [66], Yamamoto et al. [67], Gala et al. [68], Miranda de Sousa et al. [86]
Guillain-Barre syndrome	0.09–5%	Koshy et al. [35], Sil et al. [43], Hira et al. [79]	Simon et al. [71], Sharma et al. [72], Goncalves et al. [73], Fragoso et al. [74], Chen et al. [75], Esack et al. [76], Ralapanawa et al. [77], Soares et al. [78]
Mononeuropathies	0.14%	Weeratunga et al. [60]	Mazliha et al. [80], Patey et al. [81],Ratnayake et al. [82]
Cerebellitis	NA	Weeratunga et al. [84]	Withana et al. [83], Liyanage et al. [85]
Optic neuritis	NA	Weeratunga et al. [84]	Yamamoto et al. [67], Miranda de Sousa et al. [86]
Muscle dysfunction and rhabdomyolysis	NA	Misra et al. [39], Misra et al. [102]	Jain et al. [90], Jha et al. [91], Roy et al. [92], Davis et al. [93], Acharya et al. [94], Gunasekera et al. [95], Karakus et al. [96] Lim et al. [97], Sargeant et al. [98], Mok et al. [99], [100,101]
GASTROINTESTINAL			
Acute liver failure	0.4–17.4%	Jagadishkumar et al. [103],	Lum et al. [111], Arora et al. [108], Gasperino et al. [109], Jhamb et al. [110], Osorio et al. [112], Saikia et al. [113], Sirivichayakul et al. [114], Soundravally et al. [115], Vinodh et al. [116], Gupta et al. [118]
Acalculous cholecystitis	NA	Nimmagadda et al. [122], Laul et al. [41], Jhamb et al. [153]	Anam et al. [124], Das et al. [125], Kuna et al. [126]
Acute pancreatitis	NA	-	Anam et al. [127], Kumar et al. [128], Lee et al. [129], Chen et al. [130]
Bleeding gastric ulcers	3.4%	-	Neeraja et al. [25]
RENAL			
Acute kidney injury	7.3% – 13.3%	Khan et al. [135], Neeraja et al. [25], Khalil et al. [136], Mehra et al. [138]	Siriyakorn et al. [101], Jha et al. [100]
RESPIRATORY			
ARDS	NA	Wang et al. [146]	Kumar et al. [144], Patel et al. [145], Lum et al. [147]
Pneumonitis, bronchiolitis	NA	Mohamed et al. [148]	Kumar et al. [144]
Pulmonary haemorrhage	NA	Mohamed et al. [148]	Setlik et al. [149]
HAEMATOLOGICAL			
Splenomegaly	7.89% – 21.2%	Jhamb et al. [153], Pothapregada et al. [123], Pawaria et al. [151]	
Haemophagocytic lymphohistiocytosis	NA	Ellis et al. [162], Pothapregada et al. [152]	Anam et al. [124], Jasmine et al. [154], Kapdi et al. [156], Krithika et al. [157], Wiwanitkit et al. [158], Arshad et al. [159], Hein et al. [163], Koshy et al. [164], Lakhotia et al. [165], Mitra et al. [166], Raju et al. [169], Ray et al. [170], Sharp et al. [171],
Aplastic anaemia	NA	-	Ramzan et al. [173]
Thrombotic thrombocytopaenic purpura	NA	-	Gavali et al. [175], Deepanjali et al [174]

NA: not available, ADEM: acute demyelinating encephalomyelitis, ARDS: acute respiratory distress syndrome

involvement with metabolic derangement, i.e. metabolic acidosis, hepatic failure, disseminated intravascular coagulation, prolonged shock, severe hyponatremia or brain haemorrhage. In a retrospective study done in Thailand, of 1493 children admitted with dengue, 80 children (5.4%) were identified to have neurological manifestations of some sort [42]. Of these 80 children, 83.3% presented with altered consciousness, 45.2% with seizures and 21.4% showed nuchal rigidity. There was only one case of histologically confirmed dengue encephalitis in this series, as an autopsy finding. In all cases, neurological manifestations occurred while the patients were still febrile. Another retrospective study from India reported 15% patients with encephalopathy [39]. This study further showed that CNS involvement was commoner in patients with DHF and DSS, and DENV2 and DENV3 were the commonest aetiological agents.

There is evidence to suggest that the dengue virus is neurotropic. In a prospective study of 21 serologically proven dengue cases, 10 showed dengue PCR positivity in CSF, and 9 out of 21 were diagnosed as dengue encephalitis [36]. The understanding of neurotropic effects of the dengue virus has introduced a relatively new entity called dengue encephalitis in the past decade. It is defined as dengue with CNS involvement and the presence of dengue RNA, IgM, or NS1 antigen in CSF, and CSF pleocytosis without other neuroinvasive pathogens. In a prospective case control study of 27 patients with encephalopathy, CSF analysis was normal in all, however 64% showed positive dengue specific IgM, indicating possible viral invasion of the CSF [45]. However, in the study of 80 children in Thailand mentioned above, dengue specific IgM and dengue RNA PCR was not detected in the available CSF specimens [42]. Cerebral oedema was demonstrated on magnetic resonance imaging (MRI) of the brain in the majority, with only two patients showing scattered focal lesions. Imaging-proven dengue encephalitis is seldom reported [46].

Meningitis is uncommon in dengue fever. Two patients presenting with classic features of meningitis, i.e. fever, headache and neck stiffness have been reported in dengue infection, without the typical features of dengue fever [47].

Intracranial haemorrhages have been infrequently reported [38,48–51]. Intracerebral haemorrhage, subarachnoid haemorrhage and subdural haemorrhage have been described. In a case series of nine patients with intracranial haemorrhage, fever, vomiting and altered level of consciousness were the common presenting complaints [50]. The outcome in patients with intracranial haemorrhage was poor; 5 patients died, while 3 were discharged, one was left with a Glasgow outcome scale of 3. Importantly, haemorrhages were associated with a thromboctytopenia of >20,000/mm^2, emphasizing the fact that brain imaging should be considered in dengue patients with loss of consciousness without severe thrombocytopaenia. An unusual case of subdural effusion in a 50-year-old man with dengue fever has been described [51]. The patient has presented four days after discharge with sudden onset headache, generalized tonic-clonic fits and altered sensorium. CT of the brain showed bilateral frontal lobe subdural effusions which was later confirmed by MRI. The patient recovered fully by the sixth day of illness.

Spinal cord involvement is rare. Several cases of transverse myelitis [52–61] have been described from China, Thailand, India, Singapore and Brazil. An 8-month-old child who developed acute diffuse transverse myelitis was reported from India, who recovered with corticosteroid treatment [57]. A cluster of patients with acute transverse myelitis has been reported from the Brazilian Amazon region [54]. Whether this outbreak was related to unique epidemiological factors or a particular strain of DENV is not known, although such clustering of cases has not been reported elsewhere. CSF findings in these cases have been largely normal, suggesting a post-infectious immune mediated aetiology.

Acute demyelinating encephalomyelitis (ADEM) has also been described in dengue, in several case reports [62–70]. Demyelinating lesions involving the spinal cord, periventricular white matter, corona radiata, thalami, corpus callosum, hippocampus, brainstem, and cerebellum have been observed on magnetic resonance imaging. In one autopsy, demyelination, macrophage infiltration and perivascular lymphocytic infiltration, with foci of haemorrhage have been demonstrated [69].

Peripheral nervous system is involvement has been described in dengue, both as mononeuropathies and demyelinating polyneuropathy. Guillain-Barre syndrome, characterized by acute flaccid paralysis, has been reported as a presenting feature of dengue as well as a post infectious immune phenomenon [35,43,71–79]. A case series of three patients presenting with classical features of dengue fever and developing acute onset areflexic quadriparesis on the second day of illness have been reported [71]. Diagnosis of dengue in these patients was confirmed by RT-PCR of CSF and serum. Complete recovery with intravenous immunoglobulin was seen within one week in all three patients. It is also possible that asymptomatic dengue infection could be a cause of Guillain-Barre syndrome. In one case series, patients presenting with Guillain-Barre syndrome during a dengue epidemic in Brazil were studied [78]. Of 15 patients studied, seven had IgM positivity in serum; most of these patients had no definite history of dengue-like illness. Is it possible that dengue virus infection, even asymptomatic or with minimal symptoms, maybe an aetiological factor for Guillain-Barre

syndrome. Isolated 6th cranial nerve palsy, facial nerve paralysis and diaphragmatic paralysis have been reported following dengue infection [60,80–82].

Cerebellar syndromes may also result from dengue infection; cases of acute infective as well as post infective cerebellitis have been reported, all of which have recovered completely [83,84]. There is a single report of extra pyramidal system involvement with dengue [85].

Neuro-opthalmological complications of dengue fever have been described as case reports. A case of 21 year old male with bilateral loss of vision with normal opthalmoscopy and unrecordable visual evoked potentials was reported. A diagnosis of retrobulbar neuritis has been made. His visual acuity improved to 6/18 after one year following treatment with steroids [60]. Two cases of neuromyelitis optica (NMO) following dengue fever in patients of Japanese ancestry have been describe, suggesting a possible genetic susceptibility for post dengue NMO [67,86]. There is a single report of uveitis with dengue [87].

Muscle dysfunction is known to occur with dengue [39]. This presents often with muscle weakness, which is usually mild and associated with myalgia and raised creatine kinase (CK) levels. Conversely, raised CK levels, without overt muscular weakness, have also been demonstrated in dengue [39]. Hypokalaemic muscle weakness associated with dengue has been increasingly reported [88–92]. Rhabdomyolysis has been described, sometimes with extremely high CK levels, and can result in acute renal failure and death [93–101]. An entity known as dengue associated transient muscle dysfunction (DMAD) has been suggested [102], associated with varying degrees of myalgia, muscle weakness, hyporeflexia, raised CPK; inflammatory changes were seen in muscle in some of these patients [39,102].

Gastrointestinal manifestations

Mild to moderate elevation of liver transaminases is commonly seen in dengue [103–105]. In a prospective study in India of 110 children with dengue, in whom co-infection with malaria, enteric fever and viral hepatitis were excluded, tender hepatomegaly and liver function abnormalities were commonly seen [103]. Elevation of liver transaminases was greater in patients with DHF compared to DF, and AST levels were higher than ALT levels. It is postulated that the latter maybe a result of associated myositis. Acute liver failure is rare, but is a well-recognized occurrence, with reported cases among infants as well as adults, and is generally seen within a week of onset of fever [106–116]. Another study from Pakistan showed that liver dysfunction was common, and was more commonly seen in patients with DF than DHF (38% vs.19%) [117]. According to another case series described in India, acute liver failure was seen within one week from the onset of fever, with mean peak AST at 2095 ± 933 and mean peak ALT at 1741 ± 731 [118]. Elevated bilirubin and alkaline phosphatase, and persistent nausea and vomiting, have been identified as predictors of acute liver failure among patients with high AST levels [119]. Most cases of acute liver failure recover, although a few fatalities are reported [106,111,115]. A retrospective study has, in fact, shown that children with acute liver failure due to dengue may have a better prognosis than those with liver failure due to other causes [107]. The pathogenesis of liver involvement in dengue is yet unclear; direct viral infection of hepatocytes and Kupffer cells is postulated, although immune mechanisms are also thought to play a role [120,121].

Acalculous cholecystis is a commonly reported clinical and ultrasonographic finding in dengue patients [41,122–126]. A rare case of acalculous cholecystitis, acute pancreatitis and pancytopenia occurring concomitantly in the same patient, during the same disease process has been described [124]. Acute pancreatitis is a less commonly described manifestation in dengue. A few isolated case reports are available [127–130]. A study enrolling 140 children with the objective of identifying pancreatic involvement is dengue reported enlarged pancreas and elevated amylase and lipase in 29% of patients [131].

Upper gastrointestinal bleeding due to dengue has been reported as an unusual manifestation of dengue [25,132]. An unusual case of a 45-year-old male presenting with bleeding per rectum complicating DHF has been described, in whom colonoscopy revealed diffuse mucosal oedema and ulcerations with active bleeding from rectum to caecum [133].

Renal manifestations

Acute kidney injury (AKI) is a common, but under-recognized entity in dengue fever [25,134]. Its incidence varies from 7.2 to 14.2% [135–138], with mortality rates ranging from 1.2% to 11.3% [136–138]. A retrospective study done in Pakistan identified male gender, DHF, DSS, neurological involvement, and prolonged activated partial thromboplastin time as independent predictors of the occurrence of AKI in patients with dengue [136]. Hypotension, rhabdomyolysis and haemolysis are possible causes of AKI in dengue [100,101,139]. Direct viral infection and immune complex mediated injury have been postulated as potential mechanisms of dengue induced acute kidney injury [140]. Isolated cases of acute tubular necrosis, IgA nephropathy and nephrotic range proteinuria in association with dengue have also been described [141–143].

Respiratory manifestations

Pleural effusions are commonly seen in DSS, as a manifestation of plasma leakage, and are not

considered a part of the expanded dengue syndrome. Apart from this, specific lung involvement is relatively uncommon in dengue. Acute respiratory distress syndrome (ARDS) is known to occur, sometimes as a part of multi-organ failure, and can be fatal [144–147]. In one case series of patients with dengue, ARDS was seen in 11 patients out of 606, and 8 of these patients died [146]. ARDS appears to be more common in older people, and with more severe illness, in particular liver and renal dysfunction, and when dengue is complicated by secondary bacterial sepsis [146]. Pneumonitis [148], bronchiolitis [144] and pulmonary haemorrhage [148,149] have also been reported in dengue. Whether ARDS develops as a part of the plasma leakage syndrome, or whether it is due to direct effects on the virus is unclear.

Haematological manifestations

Disseminated intravascular coagulopathy occurs in severe cases of dengue [117,150]. Splenomegaly has been detected, mostly in children with dengue infection [151–153]. Infection associated haemophagocytic lymphohistiocytosis (HLH) is a rare, important and under-recognised complication of dengue, and there are numerous case reports describing various presentations of HLH in dengue [15,124,154–172]. Persistent fever, cytopenias and multi-organ involvement occur, together with lymphadenopathy, hepatomegaly, splenomegaly and markedly elevated transaminases. HLH has many other causes, and in general has a poor prognosis, although the dengue-associated type appears, in some cases, to respond well to corticosteroid therapy [154,160,161,164–168,172]. A rare case of persistent thrombocytopenia evolving into pancytopenia, with bone marrow biopsy revealing aplastic anemia, has been described following dengue fever [173]. Dengue fever triggering thrombotic thrombocytopenic purpura has also been reported [174,175].

Limitations

Our search was confined to publications in the English language. We acknowledge that this may have resulted in papers published in other languages having been excluded. In all instances we included only studies or reports where comorbidities or dual infection may have confounded the clinical picture; however we acknowledge that these factors may not always be evident in the publications reviewed.

Conclusions

Dengue infection can result in a myriad of clinical manifestations, involving nearly every system in the body. Cardiac and neurological manifestations appear to be the most common of these, and dengue encephalitis is an important cause of death. Respiratory complications are relatively less common, and there are no reports of involvement of endocrine organs. The relationship between severity of dengue and these atypical manifestations is not fully understood, and serious complications can occur without the classical features of dengue shock. Thus, clinicians should be aware of these manifestations, particularly in areas where dengue is highly prevalent.

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References

[1] Brady OJ, Gething PW, Bhatt S, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012;6(8):e1760.
[2] Guo C, Zhou Z, Wen Z, et al. Global epidemiology of dengue outbreaks in 1990–2015: a systematic review and meta-analysis. Front Cell Infect Microbiol. 2017;7:317.
[3] WHO. Dengue guidelines for diagnosis, treatment, prevention and control Geneva2009 [cited 2017 Dec 7th]. Available from: http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf
[4] Wichmann D, Kularatne S, Ehrhardt S, et al. Cardiac involvement in dengue virus infections during the 2004/2005 dengue fever season in Sri Lanka. Southeast Asian J Trop Med Public Health. 2009;40 (4):727–730.
[5] Khongphatthanayothin A, Lertsapcharoen P, Supachokchaiwattana P, et al. Myocardial depression in dengue hemorrhagic fever: prevalence and clinical description. Pediatr Crit Care Med. 2007;8(6):524–529.
[6] Kularatne SA, Pathirage MM, Kumarasiri PV, et al. Cardiac complications of a dengue fever outbreak in Sri Lanka, 2005. Trans R Soc Trop Med Hyg. 2007;101 (8):804–808.
[7] Arora M, Patil RS. Cardiac manifestation in dengue fever. J Assoc Physicians India. 2016;64(7):40–44.
[8] Sheetal S, Jacob E. A study on the cardiac manifestations of dengue. J Assoc Physicians India. 2016;64 (5):30–34.
[9] Nigam AK, Singh O, Agarwal A, et al. Transient 2(nd) degree av block mobitz type II: a rare finding in dengue haemorrhagic fever. J Clin Diagn Res. 2015;9 (5):OD12–13.

[10] Navinan MR, Yudhishdran J, Herath S, et al. Complete heart block in dengue complicating management of shock due to both bleeding and leakage: a case report. BMC Res Notes. 2015;8:68.
[11] Virk HU, Inayat F, Rahman ZU. Complete heart block in association with dengue hemorrhagic fever. Korean Circ J. 2016;46(6):866–869.
[12] Dhariwal AK, Sanzgiri PS, Nagvekar V. High degree atrioventricular block with ventricular asystole in a case of dengue fever. Indian Heart J. 2016;68:S194–S197.
[13] Kaushik JS, Gupta P, Rajpal S, et al. Spontaneous resolution of sinoatrial exit block and atrioventricular dissociation in a child with dengue fever. Singapore Med J. 2010;51(9):e146–148.
[14] Matthias AT, Indrakumar J, Gunatilake SB. Ventricular trigeminy in a patient with serologically confirmed dengue haemorrhagic fever. Int Arch Med. 2014;7:28.
[15] Pothapregada S. Atypical manifestations of dengue fever. Indian Pediatr. 2014;51(11):937–938.
[16] Mahmod M, Darul ND, Mokhtar I, et al. Atrial fibrillation as a complication of dengue hemorrhagic fever: non-self-limiting manifestation. Int J Infect Dis. 2009;13(5):e316–318.
[17] Horta Veloso H, Ferreira Junior JA, Jm BDP, et al. Acute atrial fibrillation during dengue hemorrhagic fever. Braz J Infect Dis. 2003;7(6):418–422.
[18] Kularatne SA, Gawarammana IB, Kumarasiri PR. Epidemiology, clinical features, laboratory investigations and early diagnosis of dengue fever in adults: a descriptive study in Sri Lanka. Southeast Asian J Trop Med Public Health. 2005;36(3):686–692.
[19] La-Orkhun V, Supachokchaiwattana P, Lertsapcharoen P, et al. Spectrum of cardiac rhythm abnormalities and heart rate variability during the convalescent stage of dengue virus infection: a holter study. Ann Trop Paediatr. 2011;31(2):123–128.
[20] Kirawittaya T, Yoon IK, Wichit S, et al. Evaluation of cardiac involvement in children with dengue by serial echocardiographic studies. PLoS Negl Trop Dis. 2015;9(7):e0003943.
[21] Yacoub S, Griffiths A, Chau TT, et al. Cardiac function in Vietnamese patients with different dengue severity grades. Crit Care Med. 2012;40(2):477–483.
[22] Wali JP, Biswas A, Chandra S, et al. Cardiac involvement in dengue haemorrhagic fever. Int J Cardiol. 1998;64(1):31–36.
[23] Khongphatthanayothin A, Suesaowalak M, Muangmingsook S, et al. Hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage: an echocardiographic study. Intensive Care Med. 2003;29(4):570–574.
[24] Miranda CH, Borges Mde C, Schmidt A, et al. A case presentation of a fatal dengue myocarditis showing evidence for dengue virus-induced lesion. Eur Heart J Acute Cardiovasc Care. 2013;2(2):127–130.
[25] Neeraja M, lakshmi V, Teja VD, et al. Unusual and rare manifestations of dengue during a dengue outbreak in a tertiary care hospital in South India. Arch Virol. 2014;159(7):1567–1573.
[26] Li Y, Hu Z, Huang Y, et al. Characterization of the myocarditis during the worst outbreak of dengue infection in China. Medicine (Baltimore). 2016;95(27):e4051.
[27] Marques N, Gan VC, Leo YS. Dengue myocarditis in Singapore: two case reports. Infection. 2013;41(3):709–714.
[28] Tahir H, Daruwalla V, Hayat S. Myocarditis leading to severe dilated cardiomyopathy in a patient with dengue fever. Case Rep Cardiol. 2015;2015:319312.
[29] Sane S, Saulova A, McLaren R, et al. A fatal case of primary dengue infection with myocarditis and cerebral oedema. Australas Med J. 2015;8(9):299–303.
[30] Ku YH, Yu WL. Fatal dengue myocarditis despite the use of extracorporeal membrane oxygenation. Case Rep Infect Dis. 2016;2016:5627217.
[31] Lee IK, Lee WH, Liu JW, et al. Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. Int J Infect Dis. 2010;14(10):e919–922.
[32] Miranda CH, Borges Mde C, Matsuno AK, et al. Evaluation of cardiac involvement during dengue viral infection. Clin Infect Dis. 2013;57(6):812–819.
[33] Tayeb B, Piot C, Roubille F. Acute pericarditis after dengue fever. Ann Cardiol Angeiol (Paris). 2011;60(4):240–242.
[34] Bendwal S, Malviya K, Jatav OP. Cardiac tamponade presenting as early manifestation in dengue fever. J Assoc Physicians India. 2014;62(3):257–259.
[35] Koshy JM, Joseph DM, John M, et al. Spectrum of neurological manifestations in dengue virus infection in Northwest India. Trop Doct. 2013;42(4):191–194.
[36] Solomon T, Dung NM, Vaughn DW, et al. Neurological manifestations of dengue infection. Lancet. 2000;355(9209):1053–1059.
[37] Aggarwal A, Kumar P, Faridi MM. Neurological manifestation as presenting feature of dengue infection. J Pediatr Neurosci. 2015;10(1):76–77.
[38] Ahmed S, Ali N, Tariq WU. Neurological manifestations as presenting feature in dengue fever. J Coll Physicians Surg Pak. 2007;17(4):236–237.
[39] Uk M, Kalita J, Ve M, et al. Central nervous system and muscle involvement in dengue patients: A study from a tertiary care center. J Clin Virol. 2015;72:146–151.
[40] Uk M, Kalita J, Uk S, et al. Neurological manifestations of dengue virus infection. J Neurol Sci. 2006;244(1–2):117–122.
[41] Laul A, Laul P, Merugumala V, et al. Clinical profiles of dengue infection during an outbreak in Northern India. J Trop Med. 2016;2016:5917934.
[42] Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health. 2001;32(2):341–345.
[43] Sil A, Biswas T, Samanta M, et al. Neurological manifestations in children with dengue fever: an Indian perspective. Trop Doct. 2016;47(2):145–149.
[44] IKumar R, Tripathi S, Tambe JJ, et al. Dengue encephalopathy in children in Northern India: clinical features and comparison with non dengue. J Neurol Sci. 2008;269(1–2):41–48.
[45] Cam BV, Fonsmark L, Hue NB, et al. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg. 2001;65(6):848–851.
[46] Muzaffar J, Venkata Krishnan P, Gupta N, et al. Dengue encephalitis: why we need to identify this entity in a dengue-prone region. Singapore Med J. 2006;47(11):975–977.
[47] Goswami RP, Mukherjee A, Biswas T, et al. Two cases of dengue meningitis: a rare first presentation. J Infect Dev Ctries. 2012;6(2):208–211.
[48] Jayasinghe NS, Thalagala E, Wattegama M, et al. Dengue fever with diffuse cerebral hemorrhages,

subdural hematoma and cranial diabetes insipidus. BMC Res Notes. 2016;9:265.
[49] Kumar N, Gupta G, Agrawal K, et al. Neurological manifestations in dengue seropositive patients. Neurology. 2015;84(14 Supplement):P6.307.
[50] Sam JE, Gee TS, Nasser AW. Deadly intracranial bleed in patients with dengue fever: A series of nine patients and review of literature. J Neurosci Rural Pract. 2016;7(3):423–434.
[51] Bharti P, Bala K. Subdural effusion in dengue patient as a late neurological complication: a rare case report. J Clin Diagn Res. 2015;9(7):OD01–2.
[52] Mota MT, Estofolete CF, Zini N, et al. Transverse myelitis as an unusual complication of dengue fever. Am J Trop Med Hyg. 2016;96(2):380–381.
[53] Chanthamat N, Sathirapanya P. Acute transverse myelitis associated with dengue viral infection. J Spinal Cord Med. 2010;33(4):425–427.
[54] de Sousa AM, Alvarenga MP, Alvarenga RM. A cluster of transverse myelitis following dengue virus infection in the brazilian Amazon region. Trop Med Health. 2014;42(3):115–120.
[55] Larik A, Chiong Y, Lee LC, et al. Longitudinally extensive transverse myelitis associated with dengue fever. BMJ Case Rep. 2012. bcr.12.2011.5378.
[56] Mo Z, Dong Y, Chen X, et al. Acute transverse myelitis and subacute thyroiditis associated with dengue viral infection: A case report and literature review. Exp Ther Med. 2016;12(4):2331–2335.
[57] Patras E, Polagani PK, Sural A, et al. A rare case of an 8-month-old child with dengue fever complicated by acute diffuse transverse myelitis. J Pediatr Neurosci. 2016;11(3):292–293.
[58] Seet RC, Lim EC, Wilder-Smith EP. Acute transverse myelitis following dengue virus infection. J Clin Virol. 2006;35(3):310–312.
[59] Tomar LR, Mannar V, Pruthi S, et al. An unusual presentation of dengue fever: association with longitudinal extensive transverse myelitis. Perm J. 2016;19(4):e133–135.
[60] Weeratunga PN, Caldera MC, Gooneratne IK, et al. Neurological manifestations of dengue: a cross sectional study. Travel Med Infect Dis. 2013;12 (2):189–193.
[61] Fong CY, Hlaing CS, Tay CG, et al. Longitudinal extensive transverse myelitis with cervical epidural haematoma following dengue virus infection. Eur J Paediatr Neurol. 2016;20(3):449–453.
[62] Gupta M, Nayak R, Khwaja GA, et al. Acute disseminated encephalomyelitis associated with dengue infection: a case report with literature review. J Neurol Sci. 2013;335(1–2):216–218.
[63] Brito CA, Sobreira S, Cordeiro MT, et al. Acute disseminated encephalomyelitis in classic dengue. Rev Soc Bras Med Trop. 2007;40(2):236–238.
[64] Fragoso YD, Brooks JB. Encephalomyelitis associated with dengue fever. JAMA Neurol. 2016;73 (11):1368.
[65] Karoli R, Siddiqi Z, Fatima J, et al. Was it a case of acute disseminated encephalomyelitis? A rare association following dengue fever. J Neurosci Rural Pract. 2013;4(3):318–321.
[66] Viswanathan S, Botross N, Rusli BN, et al. Acute disseminated encephalomyelitis complicating dengue infection with neuroimaging mimicking multiple sclerosis: a report of two cases. Mult Scler Relat Disord. 2016;10:112–115.
[67] Yamamoto Y, Takasaki T, Yamada K, et al. Acute disseminated encephalomyelitis following dengue fever. J Infect Chemother. 2002;8(2):175–177.
[68] Gala HC, Avasthi BS, Lokeshwar MR. Dengue shock syndrome with two atypical complications. Indian J Pediatr. 2011;79(3):386–388.
[69] Sundaram C, Uppin SG, Dakshinamurthy KV, et al. Acute disseminated encephalomyelitis following dengue hemorrhagic fever. Neurol India. 2010;58 (4):599–601.
[70] Kamath SR, Ranjit S. Clinical features, complications and atypical manifestations of children with severe forms of dengue hemorrhagic fever in South India. Indian J Pediatr. 2006;73(10):889–895.
[71] Simon O, Billot S, Guyon D, et al. Early Guillain-Barre syndrome associated with acute dengue fever. J Clin Virol. 2016;77:29–31.
[72] Sharma CM, Kumawat BL, Ralot T, et al. Guillain-Barre syndrome occurring during dengue fever. J Indian Med Assoc. 2012;109(9):675, 682.
[73] Goncalves E. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome) following dengue fever. Rev Inst Med Trop Sao Paulo. 2011;53(4):223–225.
[74] Fragoso YD, Gomes S, Brooks JB, et al. Guillain-Barre syndrome and dengue fever: report on ten new cases in Brazil. Arq Neuropsiquiatr. 2016;74(12):1039–1040.
[75] Chen TY, Lee CT. Guillain-Barre syndrome following dengue fever. Ann Emerg Med. 2007;50(1):94–95.
[76] Esack A, Teelucksingh S, Singh N. The Guillain-Barre syndrome following dengue fever. West Indian Med J. 1999;48(1):36–37.
[77] Ralapanawa DM, Kularatne SA, Jayalath WA. Guillain-Barre syndrome following dengue fever and literature review. BMC Res Notes. 2015;8:729.
[78] Soares CN, Cabral-Castro M, Oliveira C, et al. Oligosymptomatic dengue infection: a potential cause of Guillain Barre syndrome. Arq Neuropsiquiatr. 2008;66(2A):234–237.
[79] Hira HS, Kaur A, Shukla A. Acute neuromuscular weakness associated with dengue infection. J Neurosci Rural Pract. 2012;3(1):36–39.
[80] Mazliha M, Boo YL, Chin PW. Isolated unilateral sixth cranial nerve palsy: A rare presentation of dengue fever. Malays Fam Physician. 2017;11(1):25–26.
[81] Patey O, Ollivaud L, Breuil J, et al. Unusual neurologic manifestations occurring during dengue fever infection. Am J Trop Med Hyg. 1993;48(6):793–802.
[82] Ratnayake EC, Shivanthan C, Wijesiriwardena BC. Diaphragmatic paralysis: a rare consequence of dengue fever. BMC Infect Dis. 2012;12:46.
[83] Withana M, Rodrigo C, Chang T, et al. Dengue fever presenting with acute cerebellitis: a case report. BMC Res Notes. 2014;7:125.
[84] Weeratunga PN, Caldera HP, Gooneratne IK, et al. Spontaneously resolving cerebellar syndrome as a sequelae of dengue viral infection: a case series from Sri Lanka. Pract Neurol. 2013;14(3):176–178.
[85] Liyanage G, Adhikari L, Wijesekera S, et al. Two case reports on thalamic and basal ganglia involvement in children with dengue fever. Case Rep Infect Dis. 2016;2016:7961368.
[86] Miranda de Sousa A, Puccioni-Sohler M, Dias Borges A, et al. Post-dengue neuromyelitis optica: case report of a Japanese-descendent Brazilian child. J Infect Chemother. 2006;12(6):396–398.

[87] Gupta A, Srinivasan R, Setia S, et al. Uveitis following dengue fever. Eye (Lond). 2009;23(4):873–876.
[88] Gupta DK, Vaish AK, Arya RK, et al. Hypokalaemic quadriparesis: an unusual manifestation of dengue fever. BMJ Case Rep. 2011. bcr.12.2010.3673.
[89] Gutch M, Agarwal A, Amar A. Hypokalemic quadriparesis: an unusual manifestation of dengue fever. J Nat Sci Biol Med. 2012;3(1):81–83.
[90] Jain RS, Gupta PK, Agrawal R, et al. An unusual case of dengue infection presenting with hypokalemic paralysis with hypomagnesemia. J Clin Virol. 2015;69:197–199.
[91] Jha S, Ansari MK. Dengue infection causing acute hypokalemic quadriparesis. Neurol India. 2010;58 (4):592–594.
[92] Roy A, Tripathi AK, Verma SP, et al. Acute hypokalaemic quadriparesis in dengue fever. BMJ Case Rep. 2011. bcr.11.2010.3514.
[93] Davis JS, Bourke P. Rhabdomyolysis associated with dengue virus infection. Clin Infect Dis. 2004;38(10):e109–111.
[94] Acharya S, Shukla S, Mahajan SN, et al. Acute dengue myositis with rhabdomyolysis and acute renal failure. Ann Indian Acad Neurol. 2010;13(3):221–222.
[95] Gunasekera HH, Adikaram AV, Herath CA, et al. Myoglobinuric acute renal failure following dengue viral infection. Ceylon Med J. 2000;45(4):181.
[96] Karakus A, Banga N, Voorn GP, et al. Dengue shock syndrome and rhabdomyolysis. Neth J Med. 2007;65 (2):78–81.
[97] Lim M, Goh HK. Rhabdomyolysis following dengue virus infection. Singapore Med J. 2005;46 (11):645–646.
[98] Sargeant T, Harris T, Wilks R, et al. Rhabdomyolysis and dengue Fever: a case report and literature review. Case Rep Med. 2013;2013:101058.
[99] Mok Y, Quah J, Siau C. A rare but potentially lethal complication of dengue. Asian Pac J Trop Med. 2013;6 (6):500–501.
[100] Jha R, Gude D, Chennamsetty S. Non-hemorrhagic dengue fever with rhabdomyolysis. Saudi J Kidney Dis Transpl. 2013;24(6):1207–1209.
[101] Siriyakorn N, Insiripong S. Fatal rhabdomyolysis in dengue hemorrhagic fever: a case report. Southeast Asian J Trop Med Public Health. 2015;46(Suppl 1):149–152.
[102] Uk M, Kalita J, Pk M, et al. Dengue-associated transient muscle dysfunction: clinical, electromyography and histopathological changes. Infection. 2012;40(2):125–130.
[103] Jagadishkumar K, Jain P, Manjunath VG, et al. Hepatic involvement in dengue fever in children. Iran J Pediatr. 2012;22(2):231–236.
[104] Kittitrakul C, Silachamroon U, Phumratanaprapin W, et al. Liver function tests abnormality and clinical severity of dengue infection in adult patients. J Med Assoc Thai. 2015;98(Suppl 1):S1–8.
[105] Kuo CH, Tai DI, Chang-Chien CS, et al. Liver biochemical tests and dengue fever. Am J Trop Med Hyg. 1992;47(3):265–270.
[106] Shah I. Dengue and liver disease. Scand J Infect Dis. 2008;40(11–12):993–994.
[107] Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health. 2009;40(1):47–53.
[108] Arora S, Nathaniel SD, Paul JC, et al. Acute liver failure in dengue haemorrhagic fever. BMJ Case Rep. 2015. bcr2015209443.
[109] Gasperino J, Yunen J, Guh A, et al. Fulminant liver failure secondary to haemorrhagic dengue in an international traveller. Liver Int. 2007;27(8):1148–1151.
[110] Jhamb R, Kashyap B, Ranga GS, et al. Dengue fever presenting as acute liver failure–a case report. Asian Pac J Trop Med. 2011;4(4):323–324.
[111] Lum LC, Lam SK, George R, et al. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health. 1993;24(3):467–471.
[112] Osorio J, Carvajal C, Sussman O, et al. Acute liver failure due to dengue virus infection. Int J Infect Dis. 2008;12(4):444–445.
[113] Saikia N, Talukdar R, Singal DK, et al. Hepatic calcification following dengue virus-induced fulminant hepatic failure. Indian J Gastroenterol. 2007;26(2):90–92.
[114] Sirivichayakul C, Sabcharoen A, Chanthavanich P, et al. Dengue infection with unusual manifestations: a case report. J Med Assoc Thai. 2000;83(3):325–329.
[115] Soundravally R, Narayanan P, Bhat BV, et al. Fulminant hepatic failure in an infant with severe dengue infection. Indian J Pediatr. 2010;77(4):435–437.
[116] Vinodh BN, Bammigatti C, Kumar A, et al. Dengue fever with acute liver failure. J Postgrad Med. 2005;51(4):322–323.
[117] Iqtadar S, Akbar N, Huma N, et al. Profile of hepatic involvement in dengue infections in adult Pakistani population. Pak J Med Sci. 2017;33(4):963–967.
[118] Gupta V, Khandelwal B. Acute liver failure in primary dengue infection: a case series. J Assoc Physicians India. 2016;64(1):71.
[119] Kumarasena RS, Niriella MA, Ranawaka CK, et al. Predicting acute liver failure in dengue infection. Ceylon Med J. 2016;61(1):35–36.
[120] Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg. 2006;100(7):608–614.
[121] de Macedo FC, Nicol AF, Cooper LD, et al. Histologic, viral, and molecular correlates of dengue fever infection of the liver using highly sensitive immunohistochemistry. Diagn Mol Pathol. 2006;15(4):223–228.
[122] Nimmagadda SS, Mahabala C, Boloor A, et al. Atypical manifestations of dengue fever (DF) - where do we stand today? J Clin Diagn Res. 2014;8(1):71–73.
[123] Pothapregada S, Kullu P, Kamalakannan B, et al. Is ultrasound a useful tool to predict severe dengue infection? Indian J Pediatr. 2016;83(6):500–504.
[124] Anam AM, Rabbani R, Shumy F. Expanded dengue syndrome: three concomitant uncommon presentations in the same patient. Trop Doct. 2017;47 (2):167–170.
[125] Das T, Kundu AK, Maity A, et al. Acute acalculus cholecystitis in dengue fever. J Assoc Physicians India. 2014;61(10):750–752.
[126] Kuna A, Wroczynska A, Gajewski M, et al. A case of acalculous cholecystitis in the course of dengue fever in a traveller returned from Brazil. Int Marit Health. 2016;67(1):38–41.
[127] Anam AM, Rabbani R, Shumy F, et al. Subsequent pancreatitis and haemothorax in a patient of expanded dengue syndrome. Trop Doct. 2016;46(1):40–42.
[128] Kumar KJ, Chandrashekar A, Basavaraja CK, et al. Acute pancreatitis complicating dengue hemorrhagic fever. Rev Soc Bras Med Trop. 2016;49(5):656–659.
[129] Lee CY, Tsai HC, Lee SS, et al. Dengue hemorrhagic fever presenting with hemorrhagic pancreatitis and an intramural hematoma of the duodenal wall: a case

report and review of the literature. Southeast Asian J Trop Med Public Health. 2013;44(3):400–408.
[130] Chen TC, Perng DS, Tsai JJ, et al. Dengue hemorrhagic fever complicated with acute pancreatitis and seizure. J Formos Med Assoc. 2004;103(11):865–868.
[131] Setiawan MW, Samsi TK, Wulur H, et al. Epigastric pain and sonographic assessment of the pancreas in dengue hemorrhagic fever. J Clin Ultrasound. 1998;26(5):257–259.
[132] Wang JY, Tseng CC, Lee CS, et al. Clinical and upper gastroendoscopic features of patients with dengue virus infection. J Gastroenterol Hepatol. 1990;5 (6):664–668.
[133] Rama Krishna AK, Patil S, Srinivas Rao G, et al. Dengue fever presenting with acute colitis. Indian J Gastroenterol. 2006;25(2):97–98.
[134] Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health. 2007;12 (9):1087–1095.
[135] Khan Y, Sarriff A, Khan AH, et al. Prevalence and associated complication of acute kidney injury among dengue patients. Value Health. 2014;17(7):A811.
[136] Khalil MA, Sarwar S, Chaudry MA, et al. Acute kidney injury in dengue virus infection. Clin Kidney J. 2012;5 (5):390–394.
[137] Mallhi TH, Khan AH, Adnan AS, et al. Incidence, characteristics and risk factors of acute kidney injury among dengue patients: a retrospective analysis. PLoS One. 2015;10(9):e0138465.
[138] Mehra N, Patel A, Abraham G, et al. Acute kidney injury in dengue fever using acute kidney injury network criteria: incidence and risk factors. Trop Doct. 2012;42(3):160–162.
[139] Lizarraga KJ, Nayer A. Dengue-associated kidney disease. J Nephropathol. 2014;3(2):57–62.
[140] Mallhi TH, Sarriff A, Adnan AS, et al. Dengue-induced acute kidney injury (DAKI): a neglected and fatal complication of dengue viral infection–a systematic review. J Coll Physicians Surg Pak. 2015;25 (11):828–834.
[141] Mohsin N, Mohamed E, Gaber M, et al. Acute tubular necrosis associated with non-hemorrhagic dengue fever: a case report. Ren Fail. 2009;31(8):736–739.
[142] Upadhaya BK, Sharma A, Khaira A, et al. Transient IgA nephropathy with acute kidney injury in a patient with dengue fever. Saudi J Kidney Dis Transpl. 2010;21(3):521–525.
[143] Hebbal P, Darwich Y, Fong J, et al. Nephrotic-range proteinuria in an eight-year-old traveler with severe dengue: case report and review of the literature. Travel Med Infect Dis. 2016;14(1):45–48.
[144] Kumar N, Gadpayle AK, Trisal D. Atypical respiratory complications of dengue fever. Asian Pac J Trop Med. 2013;6(10):839–840.
[145] Patel HL, Patel D, Nikam AA. Dengue haemorrhagic fever with acute respiratory distress syndrome. J Assoc Physicians India. 2016;64(1):116.
[146] Wang CC, Liu SF, Liao SC, et al. Acute respiratory failure in adult patients with dengue virus infection. Am J Trop Med Hyg. 2007;77(1):151–158.
[147] Lum LC, Thong MK, Cheah YK, et al. Dengue-associated adult respiratory distress syndrome. Ann Trop Paediatr. 1995;15(4):335–339.
[148] Mohamed NA, El-Raoof EA. braheem HA. Respiratory manifestations of dengue fever in Taiz-Yemen. Egypt J Chest Dis Tuberculosis. 2013;62(2):319–323.
[149] Setlik RF, Ouellette D, Morgan J, et al. Pulmonary hemorrhage syndrome associated with an autochthonous case of dengue hemorrhagic fever. South Med J. 2004;97(7):688–691.
[150] Sosothikul D, Thisyakorn U, Thisyakorn C. Hemostatic studies in dengue patients. Southeast Asian J Trop Med Public Health. 2015;46(Suppl 1):43–45.
[151] Pawaria A, Mishra D, Juneja M, et al. Atypical manifestations of dengue fever. Indian Pediatr. 2014;51 (6):495–496.
[152] Pothapregada S, Kamalakannan B, Thulasingam M. Clinical profile of atypical manifestations of dengue fever. Indian J Pediatr. 2016;83(6):493–499.
[153] Jhamb R, Kumar A, Ranga GS, et al. Unusual manifestations in dengue outbreak 2009, Delhi, India. J Commun Dis. 2010;42(4):255–261.
[154] Jasmine YS, Lee SL, Kan FK. Infection associated haemophagocytic syndrome in severe dengue infection - a case series in a district hospital. Med J Malaysia. 2017;72(1):62–64.
[155] Joshi R, Phatarpekar A, Currimbhoy Z, et al. Haemophagocytic lymphohistiocytosis: a case series from Mumbai. Ann Trop Paediatr. 2011;31(2):135–140.
[156] Kapdi M, Shah I. Dengue and haemophagocytic lymphohistiocytosis. Scand J Infect Dis. 2012;44 (9):708–709.
[157] Krithika MV, Amboiram P, Latha SM, et al. Neonate with haemophagocytic lymphohistiocytosis secondary to dengue infection: a case report. Trop Doct. 2016;47 (3):253–255.
[158] Wiwanitkit V. Haemophagocytic lymphohistiocytosis and dengue. Acta Clin Belg. 2015;70(1):72.
[159] Arshad U, Ahmad SQ, Khan F. Hemophagocytic lymphohistiocytosis in a patient with dengue infection. Hematol Oncol Stem Cell Ther. 2015;8(4):189–190.
[160] Chung SM, Song JY, Kim W, et al. Dengue-associated hemophagocytic lymphohistiocytosis in an adult: a case report and literature review. Medicine (Baltimore). 2017;96(8):e6159.
[161] De Koninck AS, Dierick J, Steyaert S, et al. Hemophagocytic lymphohistiocytosis and dengue infection: rare case report. Acta Clin Belg. 2014;69(3):210–213.
[162] Ellis EM, Sharp TM, Perez-Padilla J, et al. Incidence and risk factors for developing dengue-associated hemophagocytic lymphohistiocytosis in Puerto Rico, 2008–2013. PLoS Negl Trop Dis. 2013;10(8):e0004939.
[163] Hein N, Bergara GH, Moura NB, et al. Dengue fever as a cause of hemophagocytic lymphohistiocytosis. Autops Case Rep. 2015;5(3):33–36.
[164] Koshy M, Mishra AK, Agrawal B, et al. Dengue fever complicated by hemophagocytosis. Oxf Med Case Reports. 2016;2016(6):121–124.
[165] Lakhotia M, Pahadiya HR, Gandhi R, et al. Stuck with pancytopenia in dengue fever: evoke for hemophagocytic syndrome. Indian J Crit Care Med. 2016;20(1):55–56.
[166] Mitra S, Bhattacharyya R. Hemophagocytic syndrome in severe dengue Fever: a rare presentation. Indian J Hematol Blood Transfus. 2014;30(Suppl 1):97–100.
[167] Pal P, Giri PP, Ramanan AV. Dengue associated hemophagocytic lymphohistiocytosis: a case series. Indian Pediatr. 2014;51(6):496–497.
[168] Phuakpet K, Sanpakit K, Vathana N, et al. Hemophagocytic lymphohistiocytosis following dengue hemorrhagic fever in Hb H/Hb Constant Spring patient. Pediatr Int. 2015;57(4):763–765.
[169] Raju S, Kalyanaraman S, Swaminathan K, et al. Hemophagocytic lymphohistiocytosis syndrome in dengue hemorrhagic fever. Indian J Pediatr. 2014;81 (12):1381–1383.

[170] Ray U, Dutta S, Mondal S, et al. Severe dengue due to secondary hemophagocytic lymphohistiocytosis: a case study. IDCases. 2017;8:50–53.
[171] Sharp TM, Gaul L, Muehlenbachs A, et al. Fatal hemophagocytic lymphohistiocytosis associated with locally acquired dengue virus infection - New Mexico and Texas, 2012. MMWR Morb Mortal Wkly Rep. 2014;63(3):49–54.
[172] Yoshifuji K, Oshina T, Sonokawa S, et al. Domestic dengue infection with hemophagocytic lymphohistiocytosis successfully treated by early steroid therapy. Rinsho Ketsueki. 2016;57(7):864–868.
[173] Ramzan M, PrakashYadav S, Sachdeva A. Post-dengue fever severe aplastic anemia: a rare association. Hematol Oncol Stem Cell Ther. 2012;5(2):122–124.
[174] Deepanjali S, Naik RR, Mailankody S, et al. Dengue virus infection triggering thrombotic thrombocytopenic purpura in pregnancy. Am J Trop Med Hyg. 2015;93(5):1028–1030.
[175] Gavali AS, Shelgaonkar J, Bartakke S. Thrombotic thrombocytopenic purpura in a case of dengue fever: a rare presentation. Indian J Crit Care Med. 2017;21(4):226–228.