Journal of Nephrology and Kidney Diseases
Volume 3 | Issue 1
ISSN: 2455-7633

Research Article Open Access

Dengue Hemorrhagic Fever and Rapidly Progressive Glomerulonephritis (RPGN): A New Persuasion

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Citation: LGomes RR (2022) Dengue Hemorrhagic Fever and Rapidly Progressive Glomerulonephritis (RPGN): A New Persuasion. J Nephrol Kidney Dis 3(1):102

Abstract

Dengue is a prevalent arthropod-borne viral disease in tropical and subtropical areas of the globe. Dengue clinical manifestations include asymptomatic infections; undifferentiated fever; dengue fever, which is characterized by fever, headache, retro orbital pain, myalgia, and arthralgia; and a severe form of the disease denominated dengue hemorrhagic fever/dengue shock syndrome, characterized by hemoconcentration, thrombocytopenia, and bleeding tendency. However, atypical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reported called expanded dengue syndrome. The renal complications of dengue virus infection cover a wide spectrum of manifestations from acute kidney injury to glomerular injury with nephritic/nephrotic syndrome. Majority of cases remain symptom free and show full recovery. We report a 55 years old lady with atypical and rare presentation of dengue disease marked by rapidly progressive glomerulonephritis. Condition improved after initial 5 days pulse methylprednisolone followed by oral prednisolone therapy and mycophenolate mofetil. The main mechanism of dengue glomerulonephritis is still unknown though both direct viral infection and immune mediated damage have been suggested to be the cause. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for renal complications in patients with dengue illness and should manage this accordingly.

Keywords: Glomerulonephritis, Thrombocytopenia, Expanded Dengue Syndrome, Dengue Fever, Acute Kidney Injury

Introduction

Dengue, an arthropod-borne viral infection of humans, is endemic to tropical and subtropical regions of the world and represents an important public health problem. Dengue viruses are transmitted by the bite of the Aedes aegypti mosquito infected by the one of the four dengue virus serotypes: dengue-1, -2, -3, and -4. More recently, dengue disease has spread geographically to many previously unaffected areas and, as travelling around the world has become more accessible, physicians in temperate areas are more likely to see returning travelers with dengue infection [1,2].

World Health Organization (WHO) classification of symptomatic dengue infection, continuously evolved, first in 1997 it divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 it improved into dengue with or without warning signs and severe dengue [3]. However, in 2011, WHO Regional Office for South East Asia (SEARO) revised and further improving the classification, divided into DF, DHF without shock or with shock (DSS) characterized by increased vascular permeability, thrombocytopenia (platelets <100,000), bleeding tendency, and, in a small percentage of patients, circulatory shock [4-7]. and expanded dengue syndrome [8].

Expanded dengue syndrome is a new entity added to the classification system to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems that had been reported including gastrointestinal, hepatic, neurological, cardiac, pulmonary and renal systems [8].

The involvement of kidneys commonly manifests as acute kidney injury caused by plasma leakage syndrome or myoglobinuria [9,10]. A proportion of cases suffer from hematuria and/or nephrotic range proteinuria, believed to be caused by a 'glomerulonephritic process' that has not been fully pathologically characterized [11]. Unlike other viral infections, glomerulonephritis determined by dengue infection is a rare complication. We describe a 55 years old Bangladeshi lady diagnosed with rapidly progressive glomerulonephritis as a part of expanded dengue syndrome caused by oligosymptomatic dengue infection.

Case Report

A 55 years old lady from rural Bangladesh, not known to have any diabetes mellitus, hypertension, bronchial asthma, coronary artery disease or kidney disease presented to us with the history of high grade, intermittent fever, severe headache, body ache and retro orbital pain for 4 days, vomiting for several times for the same duration, decreased urinary output with high colored urine and swelling of whole body for two days. She denied any cough, chest pain, palpitation, shortness of breath, abdominal pain, burning micturition, joint pain. She had no recent history of travel of late. She lives in tin shaded house in rural Bangladesh and frequently assisted her husband in field work. Her younger brother just recovered from dengue 1 week prior her illness. On examination, she was conscious, oriented, irritable, febrile (temperature 104oF), with pulse 120 beats/min, with normal rhythm and volume, blood pressure was 170/100 mm of Hg. There was diffuse blanching erythema, more prominent over trunk. There was puffiness of face and bilateral pedal edema. Other systematic examination revealed no abnormalities.

Test names (Reference range)	Day 1	Day 2	Day 4	Day 5	Day 7
Hb (12-16 gm/dl)	12	12.8	13.6	11.8	11.9
TC WBC (3500-11000/mm3)	3700	3150	2320	4600	5100
Platelet(150000-450000/mm3)	130000	92000	23000	67000	178000
PCV (35-47%)	37.1	40	48	44	36.5
SGOT (10-45 U/L)	315	404	458		96
SGPT (10-50 U/L)	218	387	412		69
Blood urea (15-40 mg/dl)	21	40	26.5		28
S. Creatinine (0.6-1.2 mg/dl)	7.89	8.2	4.7		1.86
S. Sodium (135-145 mmol/L)	130	141	136		140
S. Potassium (3.55mmol/L)	6.8	5.7	3.7		4.3
S. Albumin (3.5-5.0 g/dl)	2.8		3.3		3.8
Blood glucose (<7.8 mmol/L) Non fasting cholesterol(mg/dl)	7	5.7	6.9 96		5.9
C-reactive protein (<6 mg/L)	18		28		5
S. LDH (140-280U/L) ICT for malaria Blood film for malarial parasite Blood Culture Dengue NS1 antigen	Negative Negative No growth Positive	210			

Table 1: Day count is as per hospital stay

She was started treatment with anti-emetic, anti pyretic, intravenous loop diuretics frusemide, anti- hypertensive enalapril 10 mg once daily and pulse intravenous methylprednisolone therapy 1 gram daily. Her auto immune workup was nonconclusive (negative ANA, c- ANCA, p-ANCA) but C3 was low (0.24g/L, normal- 0.88 to 2.01 g/L). Urine routine examination showed pus cell 12-15/HPF, RBC-plenty/HPF, granular casts (++), protein (++). Phase contrast microscopy showed 27% dysmorphic RBC. 24 hours urinary total protein was 1.86 gram/day. Immunosuppression with mycophenolate mofetil (MMF) was added. Pulse steroid was continued for 5 days. She became afebrile the next day. With conservative management he showed dramatic improvement in following 5 days with reduced vomiting, anasarca and improving urinary output and general well being. Serial complete blood count was done which showed progressive improvement of her white cell and platelet counts. Oral prednisolone was started. Follow up urine routine examination prior discharge revealed 2-4 pus cell/HPF, 1-2 RBC/HPF, no casts and trace proteinuria. She was discharged on the eleventh day of illness with complete recovery with normal blood pressure with the plan to gradual tapering of oral steroid, prednisolone over next 3 months and continue MMF up to 6 months. She was found to be well on subsequent outpatient door follow-up after 3 months. Her urine examination and renal function tests were within normal range.

Discussion

Dengue is a worldwide public health problem and causes innumerous deaths. More than 40% of the world's population lives in dengue endemic areas, and the World Health Organization estimates that about 2.5 billion people in 100 countries are at risk of infection and that as many as 100 million people are infected by dengue viruses every year. In the majority of infected people, dengue is an auto-limited disease that resolves in 5-7 days. However, approximately 500,000 people develop a severe form, leading to about 20,000 deaths annually. Consequently, approximately 0.5% of dengue patients develops a severe form and requires a specialized treatment [2,12].

Dengue virus infection is a disease that found in children and adults with the main symptoms of fever, muscle and joint pain that usually worsens after the first three days. This disease is an acute febrile illness accompanied by bleeding manifestations with potential shocking and can lead to death in children<15 years, but not likely to attack adults.13 Signs of this disease are sudden high fever 2 to 7 days with no obvious cause, weakness, lethargy, anxiety, heartburn, accompanied by signs of bleeding in the skin (petechiae), bruising (ecchymosis) or rash (purpura).Sometimes there are other spontaneous bleeding manifestations such as nosebleeds, bleeding gums to dysentery. Severe symptoms can lead to decreased awareness or shock [14].

Laboratory results in dengue fever are found in thrombocytopenia (20% of the baseline on dengue hemorrhagic fever is a sign of plasma. Serological tests results in dengue are influenced by the type of dengue infection, whether it is the primary/first, or secondary/reinfection. IgM antibodies are detectable by days 3-5 after the onset of illness, rise quickly in two weeks and decline to undetectable levels after 2-3 months, because this late appearance, the first five days of clinical illness are usually negative of IgM. In dengue secondary infection, the rise of IgM are not as high as primary infection, and sometimes absent / undetectable completely [15].

IgG antibodies in primary infection, evolves relatively slow, with low titers 8-10 days after fever onset, increase subsequently and remain for many years, whereas in secondary infection it evolves rapidly, with high titers soon after fever onset and persist to a lifelong period. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Ratio of IgM/IgG titer less than 1.2 is considered a secondary dengue infection. But to be noted, titer ratio only could be validly use as a data if the IgG/IgM serological test is using pure quantitative means, not by qualitative or semi-quantitative [16].

NS1 antigen detection is widely used and cost-effective, NS1 could be detected from day 1-8 of fever onset, unaffected by a primary or secondary dengue infection. In conclusion, by combining the serological (IgG and IgM) and NS1 tests, clinicians could rapidly assess the dengue diagnosis with its types (primary or secondary infection) and applies the best treatment [17].
In 2011, based on many reports of cases with dengue-related unusual manifestations and organ complications, WHO-SEARO further improved and revised 2009 WHO guidelines by adding a new entity, that is expanded dengue syndrome (unusual/atypical manifestation of dengue), these include neurological, hepatic, renal, cardiac and other isolated organ involvement, that could be explained as complications of severe, profound shock or associated with underlying host conditions/diseases or co infections [8].
Dengue is also attributed to induce kidney in various forms. Renal disease in dengue, presenting as renal failure, is atypical but should not be overlooked. In a report, 4% of cases with acute renal failure (ARF) in a hospital in a tropical country was due to dengue infection [18]. Renal failure is a common cause of death in dengue fever [9,19]. Khalil et al found that dengue patients with renal failure had a high mortality; 100% in their case series [20]. The interesting issue is the underlying pathogenesis of renal problem in dengue, which is not well understood. There are many possibilities. The renal disease might be due to direct viral invasion of the kidney or the consequence of hemodynamic fluctuation in its clinical course. In patients with dengue and shock, it is easy to understand the involvement of the kidneys. However, in cases without shock, renal failure can still occur. In such cases, rhabdomyolysis might be the cause of acute tubular necrosis [21-23]. Adding to the non-immunologic mechanisms, immunologic mechanisms might also play a role.

The commonly reported renal involvement in dengue viral infection is acute tubular injury due to hypovolemic shock, direct cytopathic effect of the virus on renal tubules, acute thrombotic microangiopathy or damage caused by myoglobinuria [9]. Rarely acute thrombotic microangiopathy is the cause of renal dysfunction [24]. The glomerular disease with significant proteinuria leading to nephrotic syndrome is also encountered and its pathology often described simply as 'proliferative glomerulonephritis' without proper morphological description or classification of the lesion [11]. Some case reports have assumed the presence of glomerular lesions based on findings on urine analysis [25].

The role of immune complexes in causing glomerular injury in human dengue viral infection (DVI) is a subject of debate in the literature although experimental animal studies have confirmed it [26]. Some authors, while acknowledging the formation of immune complexes in DVI, have either ruled out or raised the possibility of immune complex induced glomerular injury in humans [27,28].

Glomerulonephritis in dengue fever is usually of mesangial proliferative type 9 and sometimes kidneys are involved due to systemic immune mediated inflammatory response. Proteinuria is seen in 74% of patients with DHF, [24] sometimes even to nephrotic range proteinuria [30]. In another study the prevalence of proteinuria in dengue was up to 30% [31]. Our patient had hematuria and proteinuria suggesting a possible glomerular inflammation.

Rapidly progressive glomerulonephritis (RPGN) is a syndrome of the kidney that is characterized by a rapid loss of kidney function, (usually a 50% decline in the glomerular filtration rate (GFR) within 3 months) [5] with glomerular crescent formation seen in at least 50% [5] or 75% of glomeruli seen on kidney biopsies. If left untreated, it rapidly progresses into acute kidney failure [6] and death within months. In 50% of cases, RPGN is associated with an underlying disease such as good pasture syndrome, systemic lupus erythematosus or granulomatosis with polyangiitis; the remaining cases are idiopathic. Regardless of the underlying cause, RPGN involves severe injury to the kidneys' glomeruli, with many of the glomeruli containing characteristic glomerular crescents (crescent-shaped scars). Most types of RPGN are characterized by severe and rapid loss of kidney function with marked hematuria; red blood cell casts in the urine; and proteinuria sometimes exceeding three grams in twenty-four hours, a range associated with nephrotic syndrome. Some patients also experience hypertension and edema. Severe disease is characterized by pronounced oliguria or anuria, which portends a poor prognosis.

The incidence rate of rapidly progressive glomerulonephritis is approximately 3.9 individuals per million [35]. RPGN can be classified into three types, based upon the immunofluorescence patterns:

Type I: Accounting for approximately 20% of RPGN, type I RPGN, also called anti-GBM glomerulonephritis, is characterized by the presence of autoantibodies directed against type IV collagen (specifically, the non-collagenous region of its α3 chain) [2] in the glomerular basement membrane (GBM). Some cases are associated with antibodies directed against the basement membrane of lung alveoli, producing Goodpasture syndrome. The majority of type I disease, however, features anti-GBM antibodies alone; these cases are considered idiopathic [2].

Type II: Characterized by deposition of immune complexes in glomerular tissues, type II RPGN accounts for 25% of cases. Any immune complex disease-including systemic lupus erythematosus, acute proliferative glomerulonephritis, Henoch-Schönlein purpura, and IgA nephropathy-that involves the glomerulus may progress to RPGN if severe enough.

Type III: Also known as pauci-immune RPGN, type III RPGN accounts for 55% of RPGN and features neither immune complex deposition nor anti-GBM antibodies. Instead, the glomeruli are damaged in an undefined manner, perhaps through the activation of neutrophils in response to ANCA. Type III RPGN may be isolated to the glomerulus (primary or idiopathic) or associated with a systemic disease (secondary). In most cases of the latter, the systemic disease is an ANCA-associated vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis.

Serum analysis often aids in the diagnosis of a specific underlying disease. The presence of anti-glomerular basement membrane (GBM) antibodies suggests type I RPGN; antinuclear antibodies (ANA) may support a diagnosis of systemic lupus erythematosus and type II RPGN; and type III and idiopathic RPGN are frequently associated with anti-neutrophil cytoplasmic antibodies (ANCA)-positive serum. Impaired kidney function in an individual who has had the condition for fewer than three months is characteristic of RPGN. An ultrasonographic examination of the abdomen should be obtained. Although the presence of sediment in the urine on examination can indicate proliferative glomerulonephritis, many cases of rapidly progressive glomerulonephritis need

a renal biopsy to make a diagnosis. Therapy consists of a combination of rituximab, corticosteroids, and cyclophosphamide, with a substitution of azathioprine for cyclophosphamide after a ninety-day initial period being another option. When remission is achieved, immunosuppressants are still used, usually corticosteroids with azathioprine or rituximab infusions.

A recent report on a case with deranged renal function and low serum complement C3 draws attention to the possibility of immunological mechanisms underlying dengue nephropathy [25]. Lizarraga and Nayer proposed that dengue infection is associated with systemic autoimmune disorders, which on rare occasions might involve the kidneys [9]. Immune complex formation has been shown in dengue [27]. In a previous study by Wiwanitkit, it was found that the diameter of derived complex is much smaller, compared with the diameter of glomerulus, and concluded that immune-complexes may not have a significant role in the pathogenesis of renal failure in dengue infection [27]. This means that immune-complex-induced renal disorders may not be found in dengue fever [27]. On the other hand, it is possible that there might be some underlying renal disorders that might allow immune complexes to cause renal involvement. Of interest, there are some reports on immune-complex-induced renal disorder in dengue patients with the underlying renal problems [32,33]. A good example is the previous case report on transient IgA nephropathy with acute kidney injury in a patient with dengue fever [33]. In this case report, dengue related renal damage was immune-complex mediated; mesangial IgA-dominant immune complex deposits could be detected on kidney biopsy [34]. The transient observation of immune induced nephropathy in this case might be due to the reduced ability of immune-complex formation in the late phase of dengue infection [34]. Finally, there is a recent report that dengue viral infection can also aggravate other immune complex diseases such as systemic lupus erythematosus [33].

Conclusion

Renal manifestations of dengue virus infection are varied but the occurrence of RPGN is an eye-opener and requires further investigation. Immune-complex-related nephropathy is a possible pathology that should not be forgotten. We describe the well-documented occurrence of RPGN in a case with DHF who developed impaired kidney function and significant proteinuria during critical phase. The patient was satisfactorily managed with appropriate immunosuppression. We emphasize the need for a proper renal biopsy diagnosis in cases of dengue fever presenting with renal dysfunction and proteinuria.

Conflict of Interest

None declared

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