Original Article

Frequency of Capillary leak syndrome in Dengue fever Patients

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Abstract

Introduction: Dengue is a viral disease and it is spread to the world by mosquitos. It is now common in many parts of the world. The severe form of dengue fever with bleeding manifestations is called dengue hemorrhagic fever. Some of the Dengue fever patients developed a capillary leak during a critical period of illness. This study aims at determining the frequency of capillary leaks in admitted dengue fever patients in tertiary care hospitals.

Materials and Methods: The study was conducted over a period of one month from 1st October to 30th October 2019 at the department of Medicine Federal Government Polyclinic Post Graduate Medical Institute, Islamabad. This cross-sectional study comprised of 200 consecutive hospitalized (≥14 years of both gender) dengue fever patients.

Results: Capillary leak syndrome was found in 75 patients with Dengue fever. All of them were Primary Dengue Patients. Both ascites and effusion were present in 31 patients. Ascites were only found in 25 patients, Pleural effusion bilateral in 7, Right-sided pleural effusion in 11, and Left-sided in 1 patient.

Conclusion: It is concluded that capillary leak syndrome is common in dengue patients and its early diagnosis helps us in better management during a critical phase of illness with a better outcome.

Keywords: Dengue Fever, Capillary Leak Syndrome, Dengue Shock.

Introduction

Dengue is a vector-borne viral human disease across the tropical and sub-tropical regions of the world. Dengue virus is transmitted from one person to another person by the bite of female Aedes aegypti and Aedes albopictus.[1] Dengue is present worldwide with almost 128 countries are known to have dengue outbreaks. About 390 million cases occur per year.[2] Pakistan is a subtropical country having all four serotypes. Dengue can be throughout the year but an outbreak occurs between the summer to autumn season especially after the monsoon.[3] Dengue epidemic is a major public threat since 2005 following millions of people at risk. During the current year, 2019 over 25,000 dengue cases have been confirmed from across the country.[4]

There are three phases of dengue fever illness phase I is the phase of febrile illness followed by the critical phase and then there is a recovery. Patients who don't develop increased capillary permeability in transition from febrile to afebrile phase usually get better and do not enter into the critical phase.[5] The severity of capillary leak may be different in different patients and severe permeability to plasma and fluids may cause dengue shock or pleural effusion. An increase in pleural effusion may cause increased respiratory distress which is a sign of severe dengue.[6] This study is only confined to those dengue patients who had capillary leak syndrome in the critical phase of dengue.

Capillary leak syndrome is one of the big problems of severe dengue. The main features of the capillary syndrome are hemoconcentration, hypoalbuminemia, pleural effusion, ascites, and pericardial effusion. Anasarca is not a characteristic of capillary leak syndrome. Capillary leak syndrome is the main pathological factor resulting in dengue shock syndrome and dengue haemerrohgic fever. The Hematocrit in this condition is usually >40% but maybe as high as 55-60%.[7] This increase in hematocrit is because of increased leakiness to plasma in the late stage of the febrile phase and after the setting of pyrexia may remain for 24 hours to 48 hours.

Timely identification of capillary leak syndrome is important for prompt fluid replacement and indicated progression to dengue shock syndrome. The present study conducted on dengue fever patients is an attempt to describe capillary leak syndrome who were admitted.

Materials and Methods

The study was conducted at Department of Medicine, Government Polyclinic Post Graduate Medical Institute, Islamabad for the period of one month from 1st October to 30th October 2019 during an epidemic outbreak of Dengue fever in Pakistan. It included 200 consecutive confirmed dengue patients (≥14 years of both genders) who were hospitalized for management for dengue fever. Out of the total of 200 patients with Dengue fever, capillary leak syndrome was found in 75 patients. We included these 75 patients with capillary leak syndrome in this study. All these patients had a critical phase of dengue fever. Demographic data, primary or secondary dengue, dengue test report, hematocrit, platelet counts, serum albumin, chest X-ray, ultrasonography chest and abdomen data were collected and recorded on specially designed proforma.

Laboratory diagnosis methods for dengue fever include detection of dengue NS1 antigen and antibodies (IgM/IgG) or both. Primary dengue fever was diagnosed in cases that had either positive NS1 antigen or IgM antibodies or both. Secondary dengue fever was diagnosed if the patient had a positive NS1 antigen or IgM antibodies along with IgG antibodies or the presence of all three (NS1 antigen, IgM, and IgG antibodies). All patients with Dengue fever were followed for capillary leakage and other complications by physical examination and laboratory tests (including complete blood count, biochemistry, and ultrasonography of abdomen and pleural cavities.

All data were entered on a structured proforma and data was analyzed on SPSS version 21.

Results

Out of 200 patients with Dengue fever, 75(37.5%) had capillary leak syndrome. Males were 47(62.6%) and 28(37.3%) were females. The median age, age range, and male to female ratio are shown in Figure 1. The tests results for NS1, IgM, and IgG antibodies are shown in Table 2. All 75 patients (100%) were presented with dengue fever for the first time and no patient presented with dengue fever the second time. Hematocrit > 37.5% in 49(65.3%) patients and >50% in 7(9.3%) patients. Hypoalbuminemia was seen in 64(85.3%) patients. Mild thrombocytopenia in 6(8%), moderate in 13(17.3%), and severe in 56(74.6%) patients. Detail of Plasma leaks in different sites and polyserositis (31 (41.3%) are detailed in Table-3.

Ascites were present in 25 (33.3%) patients and pleural effusion was present in 19(25.3%) patients with 11(14.6%) cases having right-sided, 7(9.3%) cases having bilateral and only 1 (1.3%) cases had isolated left-sided pleural effusion. There was no mortality in our study.

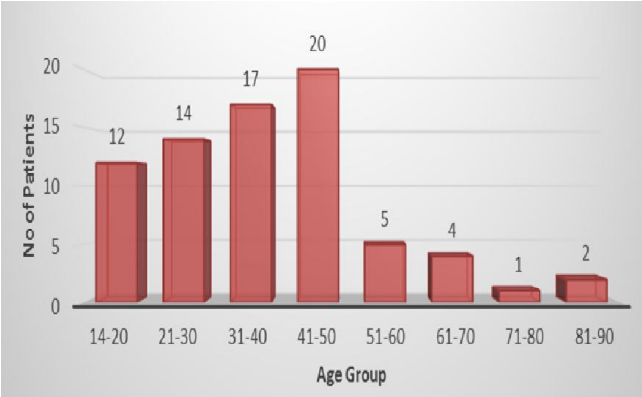

Figure 1: Age Wise Presentation (n=75)

Table 1: Laboratory Result

Dengue Serology	*NSI*	*73*	*IgM*	*02*
Hematocrit	37.5-40.0 11 (14.6%)	40.1-50.0 38 (50.6%)	50.1-60.0 07 (9.33%)	
Hypoalbuminemia	3.5-3.0 18 (24%)	2.9-2.5 38 (50.6%)	<2.5 08 (10.6%)	
Platelet count($x10^3$/cmm)	<20 32	20-50 24	50-100 13	100-150 06

Table 2: Site of Capillary Leak

Site of capillary leak	*No. of cases (%)(n=75)*
Ascites + Pleural effusion	31(41.3%)
Ascites only	25(33.3%)
Isolated right sided pleural effusion	11(14.6%)
Isolated left sided pleural effusion	01(1.33%)
Bilateral pleural effusion	07(9.33%)

Discussion

Dengue fever varies in severity and it can present just as febrile illness or with severe dengue fever disease.[8] Plasma leak which starts at the end stage of febrile illness and it may lead to dengue shock is characteristic of severe disease.[9] Capillary leak syndrome is a more common severe complication of dengue fever as compared to other feared complications which cause a lot of panic and distress such as severe bleeding and organ impairment.[10] Hematocrit ≥20%, hematocrit≤20% after fluid replacement and features such as pleural effusion, ascites, and hypoproteinemia are the hallmark of capillary leak syndrome.[11]

As hypoalbuminemia is generally not present and plasma leak is difficult to recognize that's why it is difficult to predict that those with dengue fever may have severe complications.[12,13] In our study Hematocrit level of more than 37.5 was seen in 49(65.3%) cases. Hypoaluminemia is moderate to severe in 46(61.3%) patients. Ultrasound can be used to see even a little amount of pleural effusion and ascites thus helping in detecting a capillary leak.[14] It is 100% accurate and 2009 WHO Guidelines recommend Ultrasound as a good tool for capillary leak syndrome assessment.[15] Thus Ultrasound is better than hematocrit and hypoalbuminemia to assess the presence of capillary leak syndrome early in adult dengue patients [16] In our study 75 patients were reported to have capillary leak syndrome.

According to WHO Guidelines 2009 describes severe dengue is a shock, severe bleeding, organ failure, or respiratory failure due to leakage of plasma.[17] Many studies had demonstrated the prevalence of capillary leakage on ultrasound from 34% to 100%.[18] In our study 75 cases (37.5%) out of 200 dengue hemorrhagic fever patients had a capillary leak on ultrasound.

In this study of 75 cases of capillary leak syndrome, all of them had primary dengue fever (100%). capillary leak syndrome is as frequently seen in primary as well as in secondary dengue fever.[19] The underlying mechanism of capillary leakage syndrome in dengue fever is not fully understood yet.[20]

Previously the concept was that the most severe features of dengue develop in individuals who had the previous infection of dengue with any of the strains.[21] second-time infection with another strain results in a low level of antibodies, these antibodies instead of removing the virus form an antigen-antibody complex.[22] This causes an increase in virus entry into white cells and results in enormous replication of virus which activates many folds in cytokine synthesis and activation of complement factors. The vasoactive factors produced by the macrophages lead to many fold rise in vascular permeability causing leakage of plasma, decrease in circulating volume, and shock.[23] Meltzer et al noted that secondary infection is not mandatory to develop capillary leak syndrome and the

risk of severe disease may not be increased by secondary infection.[23] In our study we have noted that it is not necessary that patients must have secondary dengue infection to develop the capillary leak syndrome or severe dengue infection.[24] The idea that secondary infection leads to an enhanced immune response which in turn causes capillary leakage in dengue fever needs further evaluation.

In the capillary leak, syndrome fluid was collected at multiple sites. In this study, Polyserositis was present in 31(41.3%) patients, followed by ascites in 25(33.3%), pleural effusion in 19(25.3%) patients. The accumulated fluid was mild to moderate in present study patients and resolved in a week's time and no particular treatment was needed.

We had some limitations in our study. As this study was conducted in a tertiary care hospital where severe cases are referred for management this may cause selection bias. Secondly, a further study is needed on a larger sample conducted at multiple centers to validate our result.

Conclusion

One of the most important things for the clinician is to recognize those patients who may progress to severe disease, so time management and hydration stop the progression of dengue fever to severe dengue fever and its complications. Early ultrasonography for capillary leak syndrome is suggested in severe dengue patients. Capillary leakage in primary dengue is as common as in secondary dengue fever.

References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013; 496:504–7. DOI: 10.1038/nature12060
2. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct 8;388(10053):1459-1544. DOI: 10.1016/S0140-6736(16)31012-1.
3. Lee TH, Lee LK, Lye DC, Leo YS. Current management of severe dengue infection. Expert Rev Anti Infect Ther. 2017 Jan;15(1):67-78. DOI: 10.1080/14787210.2017.1248405.
4. Malavige GN, Ogg GS. T cell responses in dengue viral infections. J Clin Virol. 2013 Dec;58(4):605-11. DOI: 10.1016/j.jcv.2013.10.023.
5. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Microvascular and endothelial function for risk prediction in dengue: an observational study. Lancet. 2015 Feb 26;385 Suppl 1:S102. DOI: 10.1016/S0140-6736(15)60417-2.
6. Yacoub S, Lam PK, le Vu HM, Le TL, Ha NT, Toan TT et al Association of microvascular function and endothelial biomarkers with clinical outcome in dengue: an observational study. J Infect Dis. 2016 Sep 1;214(5):697-706. DOI: 10.1093/infdis/jiw220.
7. Mongkolsapaya J, Dejnirattisai W, Xu XN, Vasanawathana S, Tangthawornchaikul N, Chairunsri A et al Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. Nat Med. 2003 Jul;9(7):921-7. DOI: 10.1038/nm887.
8. Chau TN, Quyen NT, Thuy TT, Tuan NM, Hoang DM, Dung NT et al Dengue in Vietnamese infants – results of infection-enhancement assays correlate with age-related disease epidemiology, and cellular immune responses correlate with disease severity. J Infect Dis. 2008 Aug 15;198(4):516-24. DOI: 10.1086/590117.
9. Kamaladasa A, Gomes L, Jeewandara C, Shyamali NL, Ogg GS, Malavige GN. Lipopolysaccharide acts synergistically with the dengue virus to induce monocyte production of platelet activating factor and other inflammatory mediators. Antiviral Res. 2016 Sep;133:183-90. DOI: 10.1016/j.antiviral.2016.07.016
10. Fox A, Le NM, Simmons CP, Wolbers M, Wertheim HF, Pham TK et al Immunological and viral determinants of dengue severity in hospitalized adults in Ha Noi, Viet Nam. PLoS Negl Trop Dis. 2011 Mar 1;5(3):e967. DOI: 10.1371/journal.pntd.0000967.
11. Jeewandara C, Gomes L, Wickramasinghe N, Gutowska-Owsiak D, Waithe D, et al. 2015. Platelet activating factor contributes to vascular leak in acute dengue infection. PLoS Negl Trop Dis. 2015 Feb 3;9(2):e0003459. DOI: 10.1371/journal.pntd.0003459.
12. Hottz ED, Lopes JF, Freitas C, Valls-de-Souza R, Oliveira MF, Bozza MT et al Platelets mediate increased endothelium permeability in dengue through NLRP3-inflammasome activation. Blood. 2013 Nov 14;122(20):3405-14. DOI: 10.1182/blood-2013-05-504449.
13. St John AL, Rathore AP, Raghavan B, Ng ML, Abraham SN. 2013. Contributions of mast cells and vasoactive products, leukotrienes and chymase, to dengue virus-induced vascular leakage. Elife. 2013 Apr 30;2:e00481. DOI: 10.7554/eLife.00481.
14. Trung DT, Wills B. 2010. Systemic vascular leakage associated with dengue infections – the clinical perspective. Curr Top Microbiol Immunol. 2010;338:57-66. DOI: 10.1007/978-3-642-02215-9_5.
15. Beatty PR, Puerta-Guardo H, Killingbeck SS, Glasner DR, Hopkins K, Harris E. 2015. Dengue virus NS1 triggers endothelial permeability and vascular leak that is prevented by NS1 vaccination. Sci Transl Med. 2015 Sep 9;7(304):304ra141. DOI: 10.1126/scitranslmed.aaa3787.
16. Glasner DR, Ratnasiri K, Puerta-Guardo H, Espinosa DA, Beatty PR,Harris E. 2017. Dengue virus NS1 cytokine-independent vascular leak is dependent on endothelial glycocalyx components. PLoS Pathog. 2017 Nov 9;13(11):e1006673. DOI: 10.1371/journal.ppat.1006673.
17. Wills BA, Oragui EE, Dung NM, Loan HT, Chau NV, et al. 2004. Size and charge characteristics of the protein leak in dengue shock syndrome. J Infect Dis. 2004 Aug 15;190(4):810-8. DOI: 10.1086/422754.
18. Suwarto S, Sasmono RT, Sinto R, Ibrahim E, Suryamin M. 2017. Association of endothelial glycocalyx and tight and adherens junctions with severity of plasma leakage in dengue Infection. J Infect Dis. 2017 Mar 15;215(6):992-999. DOI: 10.1093/infdis/jix041
19. Tang TH, Alonso S, Ng LF, Thein TL, Pang VJ, et al. 2017. Increased serum hyaluronic acid and heparan sulfate in dengue fever: association with plasma leakage and disease severity. Sci Rep. 2017 Apr 10;7:46191. DOI: 10.1038/srep46191
20. Chen HR, Chuang YC, Lin YS, Liu HS, Liu CC, et al. 2016. Dengue virus nonstructural protein 1 induces vascular leakage through macrophage migration inhibitory factor and autophagy. PLoS Negl Trop Dis. 2016 Jul 13;10(7):e0004828. DOI: 10.1371/journal.pntd.0004828.
21. Ferreira RA, de Oliveira SA, Gandini M, Ferreira Lda C, Correa G, et al. 2015. Circulating cytokines and chemokines associated with plasma leakage and hepatic dysfunction in Brazilian children with dengue fever. Acta Trop. 2015 Sep;149:138-47. DOI: 10.1016/j.actatropica.2015.04.023.
22. Syenina A, Jagaraj CJ, Aman SA, Sridharan A, St John AL. 2015. Dengue vascular leakage is augmented by mast cell degranulation mediated by immunoglobulin Fcγ receptors. Elife. 2015 Mar 18;4:e05291. DOI: 10.7554/eLife.05291.
23. Meltzer E, Heyman Z, Bin H, Schwartz E. Capillary leakage in travelers with dengue infection: implications for pathogenesis. Am J Trop Med Hyg. 2012 Mar;86(3):536-9. DOI: 10.4269/ajtmh.2012.10-0670.
24. Avirutnan P, Punyadee N, Noisakran S, Komoltri C, Thiemmeca S, et al. 2006. Vascular leakage in severe dengue virus infections: a potential role for the nonstructural viral protein NS1 and complement. J Infect Dis. 2006 Apr 15;193(8):1078-88. DOI: 10.1086/500949.