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View Point: Valuable use of antibody based instead of molecular based techniques for diagnosing seasonal viral outbreaks

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Abstract

Regular seasonal outbreaks of various infectious agents on the background of other sporadic diseases require confirming diagnosis of each patient for the Government health system. Initiation of any seasonal outbreak starts as sporadic cases, in remote locations which have minimal infrastructure. It is thus necessary to adopt an easier bedside methodology for detection and diagnosis. It is necessary to have appropriate infrastructure, and trained manpower for gene detection methodology. However, it is also necessary to keep in mind the cost of bedside gene detection diagnostics, especially in low budget health system. Usually in remote endemic regions, approach to the health system often causes delays in reaching the health support by the patient. In many infectious agents, the duration between the site of multiplication of infectious agent in primary and secondary symptomatic ailment, is more than one week. Thus, infectious agents get sufficient time to be cleared by the immune system. However, antibody response remains for a longer period in the form of IgM. Low cost, stability of reagents and ease in handling tests by partially trained health staff makes it easy and can alert the onset of seasonal outbreak. It is thus proposed that research on antibody methodology should be supported as a preferred method along with defined clinical symptoms. This will help public health system to contain the morbidity and possibly the spread of the outbreak.

Keywords: Viral diagnosis; Seasonal outbreaks; IgM ELISA; Gene detection.

Seasonal viral outbreaks

All over the world, seasonal outbreaks of viral diseases are dependent on rain, temperature, abundance of vector and amplifying hosts, water source, personal hygiene awareness, sanitation status and many more including the remote location. For patient, reaching the rural or primary level health system and getting accurate diagnosis is difficult even in developed countries. In countries with lesser health sources, clinical support and infrastructure for diagnosis as well as the economical condition of the patient affect the outcome and spread of the outbreak. In seasonal outbreaks all over the world each year, a set of similar clinical symptom patterns are detected in majority cases [1]. Multiple etiological agents have been detected [2] and in many cases, they remain undiagnosed [3]. In addition, in few similar clinical symptoms due to concurrent subclinical infections are also detected [2]. The background immune response in each individual, generated by subclinical infections by same or closely related viruses complicates the clinical presentation, response and diagnosis. A few examples are Dengue (DEN), Japanese Encephalitis (JE), West Nile (WN), Herpes simplex virus (HSV), Enteroviruses (EV), etc [4-8]. The changing environment conditions and rapid travel by patient to and fro from known endemic regions to newer areas also pose a problem in quick accurate diagnosis [8-11]. The problem is more amplified or intensified in severe clinical situations like Acute Encephalitis Syndrome (AES), which has at least 20 causative agents [2,3,7,12]. In India, various regions are known for their regular outbreaks [1]. Controlling few of these using preventive measures, along with vaccine coverage using the available vaccines [13, 14] is possible. Quick diagnosis leads to improving treatment modalities and has reduced few of them Influenza H1N1pmd09 [15]. Diagnosing multiple types of seasonable infectious agents from the sporadic infections at out-patient department (OPD) level or in admitted cases is a humongous load and task, especially on public health hospitals.

Current situation of diagnostic methods

It should be kept in mind that in many underdeveloped countries including some regions of India, the patient reaches the appropriate hospital having facility to receive treatment in the post-acute condition, due to lack of knowledge about prodromal symptoms, economical, transport, absence of reachable medical facility, especially in the rural regions. In contrast, in developed countries, few States and few major cities in India; awareness, approach, availability and sufficient clinical support makes it possible to get treatment during acute condition (<2-day post onset)[3].As a basic rule, acute diagnosis can be undertaken either by detecting the infectious agent by gene detection or detecting mainly the IgM antibody or rise in convalescent antibodies titer over the acute sample titer [16,17]. In post-acute condition due to difficulty in detection of the etiological agent, presence of IgM antibody is being used, and in addition it has higher specificity even in similar or cross-reactive agents [17-20]. In fact, in cases like Hepatitis E virus (HEV), Measles, Cytomegalovirus (CMV); avidity of IgM/IgG antibodies in cases due to vaccination failure and reinfection is being looked in by many scientists [18].

Molecular detection methods for sporadic and emerging infections

With the advent and ease of viral detection methodology like polymerase chain reaction (PCR) and quantitative PCR (qPCR),detection and finding genetic differences in infectious agents has gained importance [14,15,21,22]. In viral infections, which have longer duration of persistence and being a sporadic infection e.g. Respiratory Syncytial Virus (RSV), Hepatitis C virus (HCV), HSV, CMV, Rota virus genetic methodology is an accepted and proven method [12]. Use of sporadic infections like HSV,

CMV, Epstein Barr virus (EBV), *Mycobacterium tuberculosis* (M.tb) gene detection seems to be an essential method as all of them are reactivation of persistent infections. In case of surveillance of detection and typing Polio as well as non-Polio EV (NPEV), RTPCR after isolation of virus strain from stool samples lead to detection and eradication of wild type polio. However, direct RTPCR on stool sample is not used as a major diagnosis method mainly by cost and expertise. In case of emerging viruses like SARS, pandemic influenza, Ebola, Middle East Respiratory syndrome (MERS)and Nipah, detection of their respective genes by molecular means helped the detection and diagnosis [14,21]. Notably, identification of genetic detection system remains the only method in these situations thus demonstrating its importance. This is because of having defined location, symptoms and specific difference in agents. In such cases, rapid testing helped in isolating the infected individuals and controlling the spread of all these viruses H1N1, H5N1, SARS. However, in terms of cost in a large population affected by the same agent, over the years it makes it non-profitable. In case of Loop mediated isothermal amplification (LAMP) based field based test also, isolation of gene requires specific instrumentation [22]. However, usual routine influenza infections are diagnosed and managed based on clinical symptoms, especially in country like India. International network in tracking these acute viral infections with airborne capacity has been used to contain some of these seasonal infections [15]. Based on experience from Brazil during Zika virus infection, although subclinical and non-severity of Zika virus was occurring for some time, larger outbreak with altered presentation helped in detecting the emerging virus. Once subclinical infection will increase, Zika will be labeled as the seasonal outbreak like DEN.

Use of antibody based detection methods for seasonal diagnosis

The above mentioned knowledge points out that using molecular methods are suitable for localized emerging infections rather than for seasonal outbreaks. In fact, even having RTPCR methods available for JE, DEN, Hepatitis A virus (HAV), CHIK, measles, mumps, etc., antibody methods are being used even at primary health system all over world. As mentioned above, presence of IgM antibody in acute and subacute stage remains the major primary tests in these infections. IgM has an advantage of specificity as it is the first immune response and being a pentamer protein, reacting the most sensitive infectious epitopes get targeted. In many infections, severe clinical presenting disease required primary and secondary sites. In many acute infections, it takes about 3-5 or more days for presentation of clinical symptoms such as in cases of measles, mumps, AES, etc. leading to the primary test method for diagnosis [23-25]. Even in newer mutants and cross-reactive agents, only newer epitopes will be responded, generating in the form of IgM antibody response. Advent of M antibody capture (MAC) ELISA methodology for detection of IgM antibody became rapid easier and applicable even in the remote regions and serves as an accurate methodology as a first step in seasonal outbreaks [20, 23]. Basic methodology of MAC ELISA is capturing IgM from sample on pre-coated anti-human IgM antibody, followed by adding required antigen. Antigen is probed by using enzyme linked virus reactive antibody. Specificity of MAC ELISA especially for flaviviruses by using antigen source as entire virion. This leads to accessibility of specific antigenically epitopes only to pentameric IgM antibody. Further, card antibody methods are being developed for single patient's diagnosis. It should be noted here that although genetic tests are available for persistence of Hepatitis B virus (HBV), HCV and Human Immunodeficiency virus (HIV), antibody based virus detection is being used. In fact, in the age of polio eradication, IgM ELISA test has been thought as a better method of detection in newer regions of polio virus circulation [26].

In case of post outbreak, background circulation can be done only by immunological test like virus neutralization test [27].This is tested by comparing the antibody response in acute and convalescent serological response. Immune response in the form of both T and B memory cells provides the total history of the past infections. Simultaneously, record of the level of viral background circulation including response against many related viral infections as subclinical infection can be tested.

Problems and future requirement

The importance of molecular detection methodology is enormous, and has led in controlling and containing of several infectious agents e.g. Severe Acute Respiratory Syndrome (SARS), Pandemic H1N1, avian influenza, Ebola and Polio viruses. This also has importance in the initial identification of emerging infections. However, its impact on large scale seasonal vector borne infections like DEN, Chikungunya (CHIK), JE, WN, water borne Rota, NPEV and *Salmonellatyphi*is minimal.

In countries with minimal health support at the grass root level, molecular method as a basic level diagnosis is impossible due to lack of infrastructure in terms of instrumentation and trained technical manpower at the source level [20]. Additionally, because of cost, it becomes impossible for local government supported district level hospitals, to test each circulating organism to reach final diagnosis. Antibody testing by ELISA especially MAC ELISA is receiving considerable acceptance at local level. Thus, Antibody level detection, using ELISA kit or bedside investigation remains the only preferable method. This is true even in countries like India.

Future research aims

In case of both, molecular detection and antibody detection methods, indigenous kits using currently circulating viruses needs to be used. In case of MAC ELISA against flaviviruses like JE, WN, DEN, Zika, St. Luis encephalitis (SLE), Yellow Fever (YF), etc., cross reactivity and co-circulation of these viruses in same area is creating problems in differential diagnosis. MAC ELISA cross-reaction between JE and WN lead to confirming WN as emerging encephalitis only by neutralization test [8]. Newer antigens which have distinct epitopes need to be developed to reach quickly at the appropriate agent. Depending on load of background circulation of cross reactivity and subclinical infections, each kit should be checked by analyzing by sero survey of clinical, subclinical, and normal individuals in pre and post season in each region to reach utility of each kit. It is possible that in negative controls because of co-infections the cutoff might change. A regulatory system needs to be developed to approve using these kits in different areas. Research needs to be directed to develop newer detection flow through antigen methods for multiple antibodies. Similarly, using the same method detection of antigens secreted in acute infection like NS-1 for DEN can be developed for other flaviviruses. Similarly, detection of various influenza diagnosis can be developed based on specific MAbs against Influenza A, B, C epitopes rather than qPCR diagnostics. Tests to differentiate secondary infection, emerging of latent viruses like CMV, Rubella are being worked actively. This is more important for DEN serotype infections and DEN-Zika, WN-SLE, JE-WN co-infection. It will lead to mapping of ground level data all over the world, to alert various newer areas and etiological agents.

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References

1. NVBDCP (2009-2015) National Vector Borne Disease Control Programme, Govt of India. Details of AES/JE Cases and Deaths from 2009-2015, Delhi, India.
2. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, et al. (2006) Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 43:1565-1577.
3. Mittal M, Kushwaha KP, Pandey AK, Gore MM (2017) A clinico-epidemiological study of acute encephalitis syndrome with multi organ dysfunction. Int J Contemp Pediatr 4: 745-750.
4. Ansari A, Li S, Mark J Abzug MJ, Weinberg A (2004) Human Herpesviruses 6 and 7 and Central Nervous System Infection in Children. Emerg Inf Dis 10: 1450-1454.
5. Araújo F, Nogueira R, Araújo M de S, Perdigão A, Cavalcanti L, et al. (2012) Dengue in Patients with Central Nervous System Manifestations, Brazil. Emerg Inf Dis 18: 677-679.
6. Kumar A, Shukla D, Srivastava S, Idris MZ, Dhole TN (2013) High frequency of enterovirus serotype circulation in a densely populated area of India. J Infect Dev Ctries 7: 475-483.
7. Lipkin W, Hornig M (2015) Diagnostics and Discovery in Viral Central Nervous System Infections: Brain Pathology 25: 600-604.
8. Anukumar B, Sapkal GN, Tandale BV, Balasubramanian R, Gangale D (2011) West Nile encephalitis outbreak in Kerala, India. J ClinVirol 61: 152-155.
9. Dwibedi B, Mohapatra N, Rathore SK, Panda M, Pati SS, et al. (2015) An outbreak of Japanese encephalitis after two decades in Odisha, India. Ind J Med Res 142: S30-S32.
10. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, et al. (2003) Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361: 1767-1772.
11. Nuegoonpipat A, Panthuyosri N, Anantapreecha S, Chanama S, Sa-Ngasang A, et al. (2008) Cross-reactive IgM responses in patients with dengue or Japanese encephalitis. J ClinVirol 42:75-77.
12. WHO (2007) Manual for the Laboratory Diagnosis of Japanese Encephalitis Virus Infection.
13. Ranjan P, Gore M, Selvaraju S, Kushwaha KP, Srivastava DK, et al. (2014) Changes in acute encephalitis syndrome incidence after introduction of Japanese encephalitis vaccine in a region of India. J Infect 69: 200-202.
14. Chadha MS, Potdar VA, Saha S, Koul PA, Broor S, et al. (2015) Dynamics of influenza seasonality at sub-regional levels in India and implications for vaccination timing. PLoS One 10: e0124122.
15. Chadha M, Potdar VA, Saha S, Koul PA, Broor S, et al. (2012) Multisite virological influenza surveillance in India: 2004-2008. Influenza Other Respir Viruses 6:196-203.
16. Lewthwaite P, Shankar MV, Tio PH, Daly J, Last A, et al. (2010) Evaluation of two commercially available ELISAs for the diagnosis of Japanese encephalitis applied to field samples. Trop Med Int Health 15: 811-818.
17. Ravi V, Vanajakshi S, Gowda A, Chandramuki A (1989) Laboratory diagnosis of Japanese encephalitis using monoclonal antibodies and correlation of findings with the outcome. J Med Virol 29: 221-223.
18. Hübschen JM, Bork SM, Brown KE, Mankertz A, Santibanez S, et al. (2017) Challenges of measles and rubella laboratory diagnostic in the era of elimination. Clin Microbiol Infect 23: 511-515.
19. Sowers SB, Rota JS, Hickman CJ, Mercader S, Redd S, et al. (2016) High Concentrations of Measles Neutralizing Antibodies and High-Avidity Measles IgG Accurately Identify Measles Reinfection Cases. Clin Vaccine Immunol 23: 707-716.
20. Hunsperger EA, Sharp TM, Lalita P, Tikomaidraubuta K, Cardoso YR, et al. (2016) Use of a Rapid Test for diagnosis of dengue during suspected dengue outbreaks in resource-limited regions. J Clin Microbiol 54: 2090-2095.
21. Chadha MS, Comer JA, Lowe L, Rota PA, Rollin PE, et al. (2006) Nipah virus-associated encephalitis outbreak, Siliguri, India. Emerg Infect Dis 12: 235-240.
22. Kurosaki Y, Martins DBG, Kimura M, Catena ADS, et al. (2017) Development and evaluation of a rapid molecular diagnostic test for Zika virus infection by reverse transcription loop-mediated isothermal amplification. Sci Rep 7: 13503.
23. Takamatsu Y, Uchida L, Nga PT, Okamoto K, Nabeshima T, et al. (2013) An approach for differentiating echovirus 30 and Japanese encephalitisvirus infections in acute meningitis/encephalitis: a retrospective study of 103 cases in Vietnam. Virol J 10: 280.
24. Mancio J, Bettencourt N, Oliveira M, Pires-Morais G, Ribeiro VG (2013) Acute right ventricular myocarditis presenting with chest pain and syncope. BMJ Case Rep pii: bcr2012007173.
25. Wang C, You A, Tian X, Zhao M, Chen Y, et al. (2013) Analysis and solution of false-positives when testing CVA16 sera using an antibody assay against the EV71 virus. Virus Res 176: 33-36.
26. Weldon WC, Oberste MS, Pallansch MA (2016) Standardized Methods for Detection of Poliovirus Antibodies. Methods Mol Biol 1387: 145-176.
27. Tandale BV, Pawar SD, Gurav YK, Chadha MS, Koratkar SS, et al. (2010) Seroepidemiology of pandemic influenza A (H1N1) 2009 virus infections in Pune, India. BMC Infect Dis 10: 255.