

## The Growing Menace of Dengue - Is Detection and Diagnosis Enough?

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The July, 1968 issue of *Indian Pediatrics* included five original research papers related to a variety of topics; dengue and West Nile viruses, infantile tremor syndrome, sickle cell hemoglobinopathy, dermatoglyphics in congenital heart disease, and chromosomal abnormalities in measles. Given that the Dengue season is looming ahead ominously, it is not difficult to guess which study was selected this month. The somewhat lengthily entitled article 'Arthropod-borne Viral Infections in Children in Vellore, South India, With Particular Reference to Dengue and West Nile Viruses' [1] deals primarily with the establishment of diagnosis and clinical profile. Thus, we shall trace the evolution of both of these over the past five decades up to present day practice.

### THE PAST

*Historical background:* It is thought that the earliest report on dengue is found in the 'Chinese encyclopedia of disease symptoms and remedies' published during the Chin dynasty (265-420 A.D.), though at that time, it was referred to as "Water poison". This originated from the Chinese belief that the disease was caused by flying insects from the water [2]. Mysterious outbreaks of illnesses involving rashes and arthralgia in the French Carribean and Panama in the 17<sup>th</sup> century, and similar illnesses ("Knokkelkoorts" in Jakarta and "Breakbone fever" in Philadelphia) [3] in the late 18<sup>th</sup> century are now retrospectively considered to be Dengue. The current nomenclature originated during the 1827-28 West Indian epidemic, from the description in Swahili, 'Ki denga pepo', which means, "cramp-like seizure caused by an evil spirit" [3]. Later on it was speculated that the Indonesian and West Indian illnesses were most probably 'Chikungunya', while the 'Breakbone fever' was Dengue. During the 19<sup>th</sup> century, both illnesses were

reported interchangeably. Clarity was attained with successful isolation and identification of the Dengue virus in laboratory animals in the 1940s (type 1 and 2) and 1950s (type 3 and 4) [3]. That set the ball rolling and research gained momentum by the 1960s. In India, the first case of Dengue was isolated in 1956. An extensive multi-centric research study that spanned eleven years (1956-66) was funded by the Indian Council of Medical Research, the Rockefeller Foundation and the National Institute of Health, USA. The six month study (September, 1959- March, 1960) being reported in this paper was a part of this landmark endeavor.

*The study:* The authors were affiliated with the Rockefeller Foundation, Christian Medical College, Vellore and the Virus research centre in erstwhile Poona. The primary objective was to perform arboviral profiling in children under 14 years of age with febrile illnesses, followed by clinical profiling of the cases that were confirmed. The study population included 396 eligible children recruited from both urban and rural centres. Acute phase sera were inoculated in infant white mice for virological isolation, which was processed in research laboratories at Poona and the US. Subsequently 268 paired acute and convalescent sera (collected between 14 days to a few weeks) underwent serologic testing by complement fixation using different arboviral antigens, hemagglutination inhibition assay (HIA) and neutralization techniques. Dengue viruses were isolated in three children, whereas serologic evidence was found in 17 children. This clinical data was compiled with existing data from previous cases of Dengue from Vellore (1956 -1966) that had been confirmed by either virus isolation (5) or serology (9). Thus, the clinical description pertained to a total of 34 children.

It was observed that the clinical presentation in these



children was variable, though fever was a constant feature ranging from 2 to 10 days. The classically described biphasic fever was uncommon. Most children  $\leq 5$  years had associated cough, respiratory signs, and enlarged lymph nodes. Two had seizures, probably febrile. Older children ( $>5$  years) presented more commonly with the more typical features of dengue like vomiting, headache and muscle ache. Three had a morbilliform rash, two had minor bleeds and none had signs of capillary leak or shock, though four were described as having prostration (which may have been compensated shock). The absence of major bleeding and shock implies that majority had mild illness and the full spectrum of severity was not evident.

The total leukocyte count in these cases ranged from 4000-20,400 per  $\text{mm}^3$  with neutrophilic predominance. Records of platelet counts were unavailable. It is quite possible that the association with thrombocytopenia was yet to be made. The analysis of convalescent sera ( $n=251$ ) revealed positive antibody titers in 89 (35.4%) children, signifying a high prevalence of Group B arboviruses in the community. This was seen especially in those children who were older and belonged to urban areas. Circulation of multiple arboviral types was also observed on serologic testing. One set of acute and convalescent sera revealed antibodies to West Nile virus and also lead to its isolation. This was from a febrile child who had presented with facial palsy, convulsions, and coma and whose evaluation of the cerebrospinal fluid showed mononuclear predominance with normal biochemistry. The authors reported this as the first proven case of West Nile illness in India [1], as earlier reports had been based on only serology. This is probably the reason why they felt it necessary to incorporate West Nile virus into the title, though it accounted for only 0.03% of the cases. Infact, this article has received 19 citations on Google Scholar, and most of these are for the West Nile virus!

### THE PRESENT

In recent times, the magnitude of Dengue has escalated to frightening proportions. This can be exemplified by comparing a state of 34 cases over 11 years in Vellore with 9,169 cases reported in a single season (2017) in Delhi [4]. Not surprisingly, the understanding of Dengue fever has evolved considerably since Carey's paper. It is now known that the severe presentation usually occurs after secondary infection with heterologous serotypes, due to a cytokine storm [5]. Severe thrombocytopenia and capillary leakage are the hallmarks of the most life-threatening complications and death [5]. The recognition of global epidemics prompted the development of the

first World Health Organization (WHO) guidelines for management in 1975 [6]. Since then it has undergone multiple revisions, with the most recent update being released in 2012 [7]. In India, the National Vector Borne Disease Control Programme (NVBDCP) published the National Guidelines for Management of Dengue Fever in 2014, which were adapted from the 2009 and 2011 WHO guidelines on dengue [8].

The 2012 WHO guideline classified the disease as Dengue with or without warning signs (Group A and Group B respectively) and severe Dengue (Group C) [7]. The latter includes all severe cases including hemorrhage, capillary leak, hepatic failure, and encephalopathy [9]. It also serves as a case management guide with an easy-to-follow decision-making algorithm for management.

Cases of dengue fever without warning signs are advised domiciliary care with increased oral intake, antipyretics, and recognition of danger signs. Children with warning signs warrant hospitalization for monitoring of hemodynamic status coupled with judicious fluid therapy (oral or intravenous). Cases of severe dengue require emergency management with crystalloids and if need be, colloids, depending upon the type of shock, the presence of a capillary leak and/or end organ failure [7]. There is growing scientific evidence that fluid overload leads to more deaths than shock and hemorrhage [6,7].

The main implications of a laboratory diagnosis are confirmation of the clinical diagnosis (especially when there are many dengue-like illnesses) and generating epidemiological data, rather than case management. Newer virological and serologic diagnostic tools for dengue are now available that depend upon the phase of illness. Detection of the virus or its components is possible during the first five days of fever and can be done by isolation in mosquito cell-culture, detection of nucleic acid (RT-PCR and real-time RT-PCR) and detection of antigen (NS1 rapid tests, NS1 Ag ELISA, Immuno-histochemistry). Serological tests are performed after the fifth day of fever by either paired sera (ELISA, HIA, Neutralization tests) or single serum samples that can detect IgM (ELISA rapid tests) or IgG (ELISA, HIA) [7]. The antigen detection methods and IgM and IgG ELISA have the shortest turnaround time making results available within a day. NVBDCP recommends ELISA-based antigen detection tests (NS1) for diagnosis the first day onwards and antibody detection test IgM capture ELISA (MAC-ELISA) after the fifth day of onset of clinical illness [8]. Haematocrit has emerged as an important monitoring tool while

following the WHO decision-making algorithm for fluid management [9].

We have come a long way in the last 50 years. Unfortunately, the same cannot be said for the public health measures that should be undertaken to prevent this vector-borne disease. The increase in cases over the years cannot be ascribed to better clinical recognition and diagnostics. Let us hope that the new vaccine, that is currently licensed in twenty countries and indicated for individuals between 9-45 years who are dengue-seropositive [10], proves to be a better preventive strategy than curbing the breeding of mosquitoes.

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