Dengue fever: a new disease for an old continent

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Abstract

Dengue fever is an endemic disorder in many tropical areas, with a rising prevalence in the last few years. The first cases of Dengue fever in Europe date probably from 1801. Since 1928 there have been no native cases in Europe but imported ones have risen in the last few years. Recent climatic changes may allow propagation of its mosquito vector in Europe, raising concern about the propagation of this and other diseases among us.

Authors report a case of a patient admitted for fever after returning from Brazil and in whom Dengue fever was diagnosed, and review the history of this infection in Europe and several aspects concerning epidemiology, clinics, diagnostic, therapeutics and prevention of Dengue fever.

Key words: Dengue fever, Europe, Aedes, imported diseases.

Introduction

Incidence of Dengue Fever has grown dramatically over the last few years. At present more than 100 countries are deemed endemic, conditioning the risk for around 2/5 of world population and an estimate number of 50 to 100 million cases/year.[1] Although considered a tropical and subtropical countries disease, the incidence of imported cases in Europe has been growing.[2] Patients returning from endemic areas are high risk individuals to whom the diagnosis must be taken into account when there is a suggestive condition. For this, it is essential that European physicians have a comprehensive knowledge about this disorder that, although most times is self-limited, it can occasionally take very serious aspects.

Authors describe the case of an admitted patient for a febrile syndrome shortly after returning from an endemic area, having been reached a Dengue fever diagnosis.

Clinical case

A 68 years old male, Caucasian, with a history of diabetes mellitus type 2, hypertensive, dyslipidemia and pulmonary tuberculosis in childhood.

He was admitted with a fever progressing for 4 days, frontal headache and in the admittance day he had diarrhea, showing petechia in the lower limbs.

The condition started 24h after arriving from a tourism trip to Fortaleza (Brazil) where the patient had been for 21 days. During such stay he mentioned several other mosquito bites, denying any contact with stagnated water or consumption of non drinkable water.

In the objective exam, the patient was febrile (38,5ºC -101.3F), without any change on cardiopulmonary auscultation and in the abdominal exam, it was verified a palpable liver edge 2 cm – ¾ inch below the right costal edge, slightly painful to palpation. Some petechial lesions could be seen mainly in the lower limbs.

Analytically it should be pointed out in the hemogram, a leukopenia with 2100 leukocytes/mm3 and thrombocytopenia of 71.000 platelets/mL *(Table I)*. In the reminder analyses and chest X-ray there were no significant changes. Abdominal ultrasound showed a liver within normal dimensions in the upper limit and heterogeneous structure compatible with steatosis, without ascitic fluid or other changes.

During the first three admission days the fever remained continuously, ranging from 38 to 39ºC [100.4 -102.2 F], responding poorly to antipyretics and marked adynamia. Analytically, there was a bicytopenia deterioration with leukocytes 1800/mm^3 and platelets 57.000/mL, and a slight increase on transaminases with TGO 63U/L TGP 69U/L. No blood losses were recorded and the hematocrit remained stable. From the 4th day onwards (corresponding to the 8th disease day), and keeping only support therapy with serum,

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both antipyretic and analgesic, he started a progressive recovery without fever, with pain and diarrhea disappearing as well as a progressive normalization of the hemogram and transaminases *(Table I)*. On the 9th day of admission he was discharged keeping only a slight adynamia, without petechial lesions or other and with analyses within normal ranges.

Plasmodium research in thick drop, as well as the serology for Human Immunodeficiency Virus (HIV), rickettsiosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and salmonellosis were negative. Blood, stool and urine serial culture were also systematically negative.

Arbovirus serology was performed, positive for Dengue virus, serotype 2 with IgM 1/16 and IgG 1/32. The repeat at 4 weeks showed an increase on IgG titer to 1/1024 (32x higher than the baseline), thus establishing the diagnosis for Dengue fever.

TABLE 1

Main laboratory endpoints progression during admission

	Admission	3rd day	7th day
Hemoglobin (g/dL)	13,4	13,4	13,2
Hematocrit (%)	38,7	38,4	38,1
Leukocytes (absolute count)	2100	1800	11900
Neutrophils (%)	47,4	41,4	71,4
Lymphocytes (%)	35,3	41,2	20,5
Monocytes (%)	15,2	14,5	6,5
Platelets (absolute count)	71.000	57.000	200.000
Liver Transaminases			
TGO (U/L)	48	63	37
TGP (U/L)	48	69	62

Historical Perspective

Dengue fever is a long history disease. The first reference to a febrile disease in a clinical setting compatible with this entity appears in the Chinese Disease Encyclopedia published during the Chin Dynasty (265 to 420 A.C.).[3] Since then some febrile outbreaks are described, more or less compatible with Dengue fever, but only in 1780 emerges the first unequivocal description of this disease, when Benjamin Rush describes a "breaking bones" fever epidemics in Philadelphia characterized by fever, intense myalgias and arthralgias, cutaneous exanthema, hemorrhagic manifestations and prolonged asthenia while in the convalescent stage.[4]

Since then and until 1940, the disease has shown only occasionally as epidemic outbreaks. World War II would, however, revolutionize Dengue epidemiology, creating the conditions for the beginning of a big worldwide pandemia. With transmissions increasing among populations (with co-circulation of several virus serotypes) some hyperendemicity areas were established, leading to the appearance of more serious forms of the disease, namely hemorrhagic fever. The first epidemic Dengue hemorrhagic fever outbreak was described in 1953 in Manila and during the 70ties the disease became a main cause of child morbidity and mortality in Asia.[3]

Since the 80ties there has been a Dengue reappearance at global level, with the virus and its vectors expanding their geographic distribution. There are several reasons for such expansion including a fast population growth at endemic countries level, followed by bad sanitary conditions and ineffective health systems, the absence of effective measures to control mosquitoes vectors and an increase on air travelling for tropical countries.[5]

The Dengue virus and Europe

The first recorded reference to the disease in Europe dates from 1801 and emerges by the hand of the Queen of Spain. In letters written to one of her ministers, Queen Louise mentions, that after a strong rainy period by the end of May to be victim of an epidemic crossing all Madrid region, called Dengue fever[4].

In spite of the description being suggestive of such disease, the etiology of the fever attaining the Spanish Queen two centuries ago can only be assumed.

The second victim of this disease in Europe emerges in 1927 and 1928, time in which a new fever epidemic with a high percentage of hemorrhagic manifestations in European territory, more specifically in the Athens and Piraeus region. It is estimated that has reached around 650.000 citizens and caused the death to over a 1000. Serology studies enable to demonstrate that it was an infection by the Dengue virus.[6]

Since then all cases recorded in Europe, correspond as the described one to the imported cases.[2,7-10] It is thought that the real risk to a traveler to endemic

Área endémica para o Aedes aegypti (a cinzento) e para o Aedes aegypti e vírus de Dengue (a preto).

FIG. 1

diseases to get the disease is probably undervalued, partly because Dengue fever is not a compulsory statement disease, in most countries,[2] but also due to unspecified complaints, together, in our view, with a low rate of suspicion on the diagnosis by European physicians.

It is estimated that 8 to 19% of individuals look for medical assistance when coming back from tropical areas.[11] The percentage of Dengue diagnosis made in these patients where fever is the main complaint has risen by 2% in 1990 to 16% in more recent studies.[12] Most times the disease follows a benign course. However, recompiling 219 cases of imported Dengue involving 14 European countries, from 2003 to 2005, has shown a high prevalence of serious clinical manifestations reaching 11%.[13]

From the assessment of the existing data we come to the conclusion that the majority of European patients with a Dengue diagnosis were on touristic trips to endemic areas, being a risk factor a longer stay and the places visited, as most cases come from the Asian southeast.[2] Nevertheless, Latin America (including Brazil) won an increasing importance, reflecting an increase on the disease prevalence in that area and probably, also a change in the European tourism habits.[14]

A problem which has been an issue for debate for a while, concerns the possibility of disseminating the disease vector, and consequently the virus, in temperate climate areas of the world. Dengue virus is an arbovirus having humans as a reservoir and as main vector the *Aedes aegyptius*. This mosquito who has local deposits of clean water but stagnated, inhabits tropical and subtropical regions of the globe, in an distribution which can be confused with the Dengue fever, and seldom is found outside these areas[12] *(Fig. 1)*.

However, other species of the Aedes mosquitoes are able to work as disease vectors, namely *Aedes albopictus*. This mosquito is, after the *A. aegypti*, the most able vector disseminating the Dengue virus. Its presence in Europe was described for the first time in 1979, in Albania and since 1990 has been found in several Italian regions and other countries of the Mediterranean rim. [15] Since 1994 that Portugal is pointed out as a country of risk.[16] The impact on climate changes, on the mosquito possible dissemination is a controversial issue and there are no clear conclusions, although some authors admit being favorable to such view. In this case, it should be also expected the dissemination of viral diseases transmitted by it,[17] introducing the Dengue virus in regions previously free from the disease.[18] If it is the case, the Dengue can become, in a near future, a new European disease.

Clinical aspects

There are 4 known virus serotypes, each one of them offers lasting immunity, however a re-infection can happen by different serotypes.[19] As far as the clinic is concerned, the most frequent presentation is in the self-limited febrile syndrome named as Classic Dengue Fever. However, the disease spectrum ranges from the asymptomatic infection up to hemorrhagic fever and shock, with mortality reaching 50%.[19]

The Classic Dengue Fever is characterized by the sudden onset of fever, often preceded by chills, frontal and retrorbital headache, prostration and intense musculoskeletal pain (leading to the designation of "breakbone fever").[20] Fever lasts 5 to 7 days, although it can reoccur in a bimodal pattern. In about 50% patients it appears in the defervescence period, a macular or maculopapular exanthema with confluent aspect, saving small skin areas which disappear 2 to 4 days after, through a pruriginous scaling process.[12] As it happened with our patient, in some cases some minor bleeding manifestations can occur, as petechiae, epistaxis, hematuria, metrorrhagia or gastrointestinal bleeding. In laboratory it is common to occur thrombocytopenia, leukopenia, a moderate increase in transaminases and dehydrogenase lactate and hyponatremia.[12,19,20]

In about 2 to 3% of cases, the infection by the

Dengue virus evolves as hemorrhagic fever. There is a higher risk in children and individuals suffering of infection before heterologous seroimmunity. The main characteristics of Dengue Hemorrhagic Fever are the hemorrhagic phenomena and increase on capillary permeability, which shows through a decrease in the hematocrit above 20% during fluid therapy and by the occurrence of pleural effusion, ascites or hypoproteinemia[21] (Table 2). If initially the condition is indistinguishable of classic fever, after the 4th or 7th day of the disease there are early signs as central cyanosis, cold and sweaty extremities, agitation, abdominal pain and vomiting or establishment of hypothermia replacing fever.[12,19] The platelet number decreases and petechiae emerges, spontaneous ecchymosis at mucosa level, digestive tube and venopuncture sites.

It should be noticed that, as in the current case, there are hemorrhagic phenomena in the absence of an increase on vascular permeability, and they do not meet the criteria for Dengue Hemorrhagic Fever. The Tourniquet test, in spite of being included in the World Health Organization for hemorrhagic fever, has actually a low sensitivity. Is consists on inflating the sphygmomanometer cuff for 5 minutes at intermediate pressure between systolic and diastolic. The test is deemed positive when there are in the area more than 20 petechiae per 2,5 cm (inch).[2,12]

Occasionally, complications as encephalopathy, liver failure, myocardiopathy, acute respiratory distress syndrome and acalculous cholecystitis have been described.[22]

The journey history is crucial to take into account to the diagnosis. A fever starting 2 weeks after returning or lasting over 10 days excludes Dengue possibility.[12] The diagnosis might be established through the virus culture, CPR methods, or as in the current case, by serology, in which an higher increase than 4 in the IgG titer or as the case shown, by serology, where an increase above 4 in the IgG titer gives a diagnosis of certainty.[19]

The differential diagnosis includes malaria, typhoid fever, leptospirosis, West Nile virus, measles, rubella, human immunodeficiency virus seroconversion, Epstein Barr, rickettsiosis and other diseases where the initial stage can point in the direction of Dengue, namely the presence of leukopenia, which usually precede thrombocytopenia and transaminases increase.[12]

TABLE II

Dengue Hemorrhagic Fever Diagnosis Criteria according to the World Health Organization (WHO)

Fever or a history of acute febrile syndrome lasting from 2 to 7 days sometimes biphasic
Hemorrhagic manifestations Positive Tourniquet Test Petechiae, ecchymosis or purpura Bleeding from mucosae, venopuncture sites or other Hematemesis or melena
Thrombocytopenia (<100.000 cells/ mm3)
Evidence of increase vascular permeability, manifest by at least one of the following: hematocrit ≥20% of the expected value for gender and age hematocrit decrease after fluid therapy ≥20% pleural effusion, ascitis or hypoproteinemia

People traveling to endemic areas must be advised on the risk of transmission. The most adequate protection measures include the use, during the day of protecting clothing, insects repellent and insecticide, as well as limiting the existence of containers able to store water in the open air. Because the mosquito has a higher activity in the morning and in the evening, the use of mosquito nets in beds at night, thought as prophylaxis has a limited interest. As re-infection is a risk factor for the hemorrhagic form repeated trips to high endemic areas must be avoided by individuals known to have been previously infected.[12]

Conclusion

Considered until some years ago a disease limited to the tropical countries, Dengue fever seems to affect more and more Europeans, leading physicians in the old continent to be better prepared to recognize the symptoms and severity signs, in order to take the appropriate measures to meet these patients needs. ■

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