Why should pulmonologists be concerned with West Nile virus?

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It was only two years ago, in August 2010, that a cluster of West Nile virus (WNV) infections was recorded in central Macedonia in Northern Greece, placing this disease among the emerging health problems that Greek doctors are called upon to face[1,2]. Since 1937, when WNV was first isolated in Uganda, there have been numerous reports of epidemics in countries around the globe, unrelated to human race, economic capabilities, and climatic differences. Molecular virology has revealed that WNV is a single-stranded RNA virus belonging to the family of *Flaviviridae*, closely related to other human pathogens such as Japanese encephalitis, dengue and yellow fever viruses. WNV is naturally maintained in a cycle between birds and mosquitoes, but the infected saliva of the mosquito is responsible for its transmission to a wide variety of other animals and to humans[3]. In addition, there have been a few reports of transmission via the placenta, and through breast-feeding and organ transplantation.

Elucidation of the pathogenesis of the disease in humans was not easy, due to significant variation in both the viral virulence and the spectrum and intensity of the clinical manifestations in the symptomatic patients. After its inoculation into human tissues, usually into keratinocytes and Langerhans cells, the virus migrates to regional lymph nodes where it replicates. This viral multiplication is followed by a fairly mild viraemia resulting in viral dissemination to many visceral organs, where a second round of replication takes place. The viral load wanes as the titer of the specific IgM antibodies increases. Laboratory diagnosis of the disease is usually based on this increase in IgM. Depending probably on the intensity of viraemia, MNV may cross the blood-brain barrier to cause the most severe clinical manifestations of the disease[4]. The viral factors affecting transmissibility, genotype alterations and its capability to adapt to diverse hosts and environments are described in detail elsewhere[5,6].

The clinical manifestations of the disease become evident after an incubation period of 2-15 days, although most of the infections (about 80%) remain asymptomatic. The vast majority of the symptomatic infections exhibit mild illness that usually lasts less than 7 days. The main symptoms include mild to moderate fever, rigors, headache, myalgia, nausea and vomiting, following which the affected individuals acquire lifelong immunity. In some cases the patients develop a papular rash on the arms, legs or trunk[7]. The most severe

form of the disease develops in only 1% of those infected (i.e., 5% of symptomatic patients) and is characterized by the signs of meningitis, encephalitis and flaccid paralysis. The intra-hospital mortality of such cases is considerable, reaching up to 10%[8]. Certain population groups are at higher risk of a severe course. Specifically patients aged over 50 years have a 20fold higher risk of neuromuscular involvement. A similar high risk is reported for individuals with a history of immunosuppression, diabetes mellitus, chronic renal failure, alcoholism, hypertension, malignant disease or other severe comorbidities[4,10]. In addition to the above conditions, there are indications that genetic factors influencing the response path of interferon are possible determinants of the degree of risk of an individual for the development of symptomatic disease and the evolution of the symptoms[11].

Currently, although several potential therapeutic agents are under investigation, no specific treatment is available and thus the management of the disease remains supportive[12]. Even worse, as a result of continuing globalization and climate change, it is expected that Europe will face an expansion of WNV-related morbidity in the future[13]. The development of an effective vaccine for human use appears feasible, since there are already effective, licensed vaccines for the treatment of horses. Identification of the human target population, so that vaccination for WNV will be cost-effective, remains an important issue[14].

Considering the above information, is there any indication for the involvement of pulmonologists in the management of WNV infection?

Certainly, it would be unrealistic to claim that chest medicine is the dominant specialty in the handling of WNV disease, but it should be stressed that:

- Management (and possibly aetiological diagnosis) of patients with severe neurological involvement and subsequent acute respiratory failure will constitute a burden on intensive care units (ICUs) and the intensivists, many of whom have chest medicine as their primary specialty. A high percentage of affected patients require mechanical ventilation, because of severely reduced level of consciousness, respiratory muscle weakness and failure of clearance of bronchial secretions. Prolonged invasive mechanical ventilation can cause a number of respiratory tract complications, such as ventilator-associated pneumonia (VAP)[15]. There is compelling evidence that in such critically ill patients, respiratory tract complications are responsible for 25% of the overall deaths from WNV, and therefore their early detection undoubtedly requires close monitoring[16]. According to a retrospective study of 32 patients with flaccid paralysis due to WNV infection, 3 patients died during the first 4 months and 3 more by the end of one year following infection. All the deaths were attributed to respiratory complications[17]. The authors concluded that a prolonged recovery phase of those developing poliomyelitis-like syndrome was related to prolonged mechanical ventilation (mean duration 66 days) and multiple episodes of extubation and reintubation, and was associated with a mortality rate that reaches 50%. Noteworthy, only 28% of the patients with encephalitis, meningitis, or neuromuscular paralysis were able to leave hospital in a condition not necessitating additional support[18].
- Some rare cases develop bilateral diaphragmatic paralysis or haemorrhagic fever with multifocal intra-alveolar haemorrhage and pulmonary oedema[19,20]. For these unusual cases, the maintenance of a high level of suspicion on the part of the attending pulmonologists is very important.
- As the most frequent clinical manifestations of the disease (i.e., fever, cough, headache) resemble those of common respiratory infections, and usually affect individuals in the older age groups where other chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) are often present, the differential diagnosis between WNV infection and a typical COPD exacerbation represents a real challenge for the attending pulmonologist. The likelihood of such confusion is confirmed by a descriptive study from the USA including 228 cases of patients with WNV infection. Tobacco use was reported by 26-40%, cough in 14-18%, and dyspnoea in 14-20% of the patients, depending on the main clinical presentation of the infection[21].
- It is obvious that WNV infection can become a major destabilizing factor for patients with chronic respiratory diseases and particularly for those whose stability is fragile. Regardless of the spectrum of WNV infection and the content of supportive therapy required to re-establish respiratory sufficiency, the involvement of a respiratory disease specialist appears to be a very reasonable option.
- Finally, both the clinical picture and the severity of the disease have changed over time, being more threatening than previously reported. This phenomenon has possibly arisen from the continuous mutations of the WNV. As an example, during the first 6 decades follow-

ing its discovery, the WNV was not killing the infected birds, but this has now largely changed, and birds are dying from the disease. As for humans, the virus was in the beginning responsible mainly for the development of febrile disease in children, while neurological manifestations were substantially described only after 1994. Similarly, the characteristics of the transmission of WNV are constantly changing[22]. In this context, the continuing awareness of medical personnel, regardless of specialization, is clearly required.

In conclusion, there are substantial reasons for clinicians to better understand the pathogenesis and evolution of WNV infection, a disease that although it does not directly target the respiratory tract, renders it the epicentre of the management of its most serious complications. It is obvious that the involvement of pulmonologists in the handling of this emerging threat is not of marginal importance, but conversely, is expected to contribute, perhaps more than that of any other specialists, to the effective management of the life-threatening complications of the disease and the reduction of the considerable mortality carried by the severe forms of WNV infection.

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