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Emerging and re-emerging virus infections in neonates and young pediatric patients

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ABSTRACT

The epidemiology of virus infections has changed dramatically in Europe in recent years due to ecologic, anthropologic and biologic factors such as: i) climate modifications, ii) global exchange of goods and international travel, iii) increased immigration flux from Africa, South America, the Middle East and Asia, iv) reduction of cultivated areas, and v) emergence and re-emergence of human viruses from zoonotic reservoirs. In addition, recent technical advancements have allowed the identification of previously unrecognized autochthonous viral species. Thus, at present, the technical and cultural challenge is to recognize infections caused by viruses not normally circulating in our geographical region (both as imported cases or potential local outbreaks), sustained by recently discovered autochthonous viruses or due to recognized viruses which are no longer widespread in Western Europe due to past vaccination campaigns.

1. Introduction

The epidemiology of virus infections in Europe is not a static event, and has changed dramatically in recent years. Indeed, multiple inter-connect factors contribute to the dynamic and fast-evolving ecosystem, which includes humans and their viruses. Anthropologic factors, such as the introduction of effective vaccines against viruses responsible for poliomyelitis, measles, rubella, hepatitis A, hepatitis B, varicella-zoster, influenza A and B, as well as the adoption of vaccination programs during the second half of the 20th century has almost abolished the morbidity and mortality associated with these diseases in pediatric patients in Western Countries. However, the end of the last century was also characterized by the sudden and irreversible opening of European Countries to global exchanges of goods and international travel, with the possibility of re-emergence in Europe of "old" viral diseases as imported cases from countries without effective vaccination programs.

In addition, the recent SARS, influenza A(H1N1)pdm2009, influenza A(H7N9), MERS-CoV, and hepatitis E epidemics have underscored how quickly new zoonotic viruses can spread worldwide through international travel. Moreover, global warming has critically modified in just a few decades the environmental conditions favouring the spread, in our geographic region, of vectors carrying arthropod-borne viruses such as chickungunya virus, West Nile virus and Phleboviruses. The progressive reduction of cultivated areas, and their consequent reforestation, has allowed the increase in wild animal populations and the spread of diseases such as rabies, tick-borne encephalitis and hantavirus renal syndrome in Northern Europe. Although, the latter zoonotic viruses will unlikely have a great impact on the pediatric population (newborns in particular), outbreaks of mosquito-transmitted viruses can affect patients of all ages.

Finally, recent technical advancements have allowed the identification of previously unrecognized autochthonous viral species responsible for respiratory, gastrointestinal and neurologic diseases in pediatric patients, including newborns.

Thus, at present, the technical and cultural challenge is to recognize infections caused by viruses not normally circulating in our geographical region (both as imported cases or potential local outbreaks), sustained by recently discovered autochthonous viruses or due to recognized viruses which are no longer widespread in Western Europe due to past vaccination campaigns. The latter may re-emerge due to the expanding reservoir of susceptible individuals.

A short review of the most relevant aspects of emerging and re-emerging viral infections in pediatric patients with a special focus on newborns is presented.

2. Emerging viruses

The most important emerging virus remains the influenza A virus. There is a general perception that the 2009–2010 influenza A pandemic was clinically milder than previous pandemics. How-

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ever, the death rate during the last pandemic has recently been recalculated estimating that the 2009 global pandemic respiratory mortality was about 10-fold higher than the World Health Organization's laboratory-confirmed mortality count [1]. Although the pandemic mortality estimate was similar in magnitude to that of seasonal influenza, a marked shift toward mortality among persons <65 years of age occurred, so that many more life-years were lost [1]. Simonsen et al., could not be more precise about the fatality rate stratified by more defined age groups, but a survey by the Centers for Diseases Control, Atlanta, USA, spanning a 10-year period reported that pediatric mortality in the USA following the emergence of the influenza A(H1N1)pdm09 strain was substantially higher than that in previous and following years (http://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html).

Human metapneumovirus (hMPV) is a paramyxovirus that was first identified in the Netherlands in 2001 in respiratory secretions of young children with respiratory tract disease which were scored as negative using traditional diagnostic techniques. The identification of hMPV was made possible with the RAP-PCR (RNA arbitrarily primed PCR) technique for the identification of unknown viruses in cell culture [2]. Clinical symptoms associated with hMPV infection are similar to those caused by human respiratory syncytial virus (RSV) infection, and range from upper respiratory tract disease to severe bronchiolitis and pneumonia [2]. In addition, it was shown that by the age of five years, virtually all children are seropositive for hMPV [2]. Thus, besides RSV, a previously unrecognized paramyxovirus can support respiratory tract infections in small children. This finding has immediate diagnostic and treatment correlates, since an effective human monoclonal antibody (Palivizumab) is currently licensed for prevention and treatment of RSV infections only [3]. More recently, cross-neutralizing human monoclonal antibodies have been developed for treatment strategies with broader specificity [4].

Since the discovery of hPMV, techniques for "virus fishing" have been extensively applied allowing the identification of additional human Coronavirus strains (NL63, HKU1) responsible for respiratory syndromes in pediatric patients [5,6], and other viruses as well.

Human parechovirus 1 (HPeV-1) and HPeV-2 were first identified in the mid-1960s and classified as human enteroviruses (HEVs), specifically as echovirus 22 and 23. More recently, phylogenetic sequence analyses have shown that these viruses are genetically distinct from the entire *Enterovirus* genus, and they were reclassified as the new genus *Parechovirus* in the family *Picornaviridae* [7]. Usually, HPeV infections are asymptomatic, while less frequently they have been reported to be associated with mild respiratory and gastrointestinal syndromes in children [8]. Of note, the HPeV-3 strain appears to be endowed with greater virulence since it has been associated with sepsis-like syndromes, meningitis, and encephalitis in neonates and young infants [9–11].

Among enteroviruses, some strains, such as EV-71, are responsible for significant clinical manifestations, including large outbreaks of hand-foot-mouth disease (HFMD) in young children in Asia. In some cases, EV-71 infection has been associated with severe neurologic complications, such as brainstem encephalitis [12].

EV-C104, EV-C105, EV-C109, EV-C116, EV-C117 and EV-C118 are other enterovirus strains that have been identified in the last five years. These strains have been detected in pediatric and adult patients with acute otitis media, upper respiratory tract infections, as well as acquired pneumonia [13–17].

Sapoviruses are caliciviruses that were first discovered following an outbreak of gastroenteritis in an orphanage in Sapporo, Japan [18]. Sapoviruses are currently classified into seven genogroups (GI to GVII) and are able to infect humans, bats, sea lions, dogs and pigs. Strains belonging to GI, GII, GIV and GV genogroups are associated with gastrointestinal syndromes in young children and neonates [19].

Novel picornaviruses such as aichi virus, cosavirus, saffold virus, and salivirus [20] have also been implicated in gastrointestinal syndromes in children in Asia, Australia and Africa. The systematic use of comprehensive diagnostic panels in patients with gastrointestinal diseases [21] may allow the unexpected detection of these "exotic" viruses in patients with no history of recent travel abroad, suggesting a potential local circulation [22].

Phleboviruses are members of the *Bunyaviridae* family and are spread through the bite of *Phlebotomus papatasii*. These viruses are autochthonous in southern Europe (Spain, France, Italy and Greece) and are responsible for asymptomatic infections in most cases, while a minority of patients may experience fever and neurologic disorders. In infants, phlebovirus infection may also present as a usually self-solving meningitis. Diagnosis can be difficult due to the low awareness of this infection during the summer season in the Mediterranean region, the availability of few serologic and molecular diagnostic assays and the short duration of viremia.

3. Re-emerging viruses

In October 2013, the World Health Organization reported a cluster of acute flaccid paralysis (AFP) cases due to suspected wild poliovirus-infection in Syria. Confirmation was later made with the isolation of wild poliovirus type 1 in at least ten cases (http://www.who.int/csr/don/2013_10_29/en/). According to the European Center for Diseases Control (ECDC) Syria has not experienced indigenous cases of polio since 1995, while the last laboratory-confirmed imported case was reported in 1999. Immunization against polio has been mandatory in Syria since 1964 and the reported coverage with three doses of oral polio vaccine was above 95% in children under one year of age between 2002 and 2010. Since 2010, the health situation in Syria has progressively deteriorated due to the ongoing conflict and the decline in vaccination coverage for all vaccine-preventable diseases, including polio (http://www.ecdc.europa.eu/en/publications/Publications/RRA%20poliomyelitis%20Syria%2021%2010%202013.pdf). Furthermore, wild-type poliovirus 1 (WPV1) has been isolated from sewage and faeces of asymptomatic carriers in Israel http://www.ecdc.europa.eu/en/publications/Publications/polio-risk-assessment-transmission-in-Israel.pdf). Thus, significant concern over the risk of importation of wild polio virus to the EU and further re-establishment and transmission to Member States is shared among experts [23].

European countries have renewed their commitment to eliminate measles transmission by 2015 through the implementation of vaccination programs (http://www.euro.who.int/__data/assets/pdf_file/0008/119546/RC60_edoc15.pdf). The incidence of measles in Europe has decreased significantly since 1998, while the trend inverted in 2010 with a significant increase in the number of cases. The total number of reported measles cases in Europe was 30,265 in 2010, 30,567 in 2011 and 8,230 in 2012 bringing the incidence of this disease to 16.2 cases per million in the last year of surveillance (http://www.ecdc.europa.eu/en/healthtopics/measles/epidemiological_data/Pages/Number-of-measles-cases-2011.aspx). The increase in 2010 was primarily due to a large outbreak in Bulgaria with more than 24,000 reported cases and 24 deaths affecting mainly infants, children and young adults [24]. Re-emergence of measles in Europe is due to multiple social, psychological and behavioural factors, including a lower perception of the risks associated with the disease, the growing (unmotivated) fear of vaccination-associated adverse events, ethnic and religious traditions, which have led to the accumulation over time of a susceptible population.

4. Conclusions

Our understanding of viruses has recently been improved by the identification of new virus species, the increased awareness that zoonotic viruses can cross the species-barrier more frequently than previously thought and the realization that viruses can spread much faster in a globalized world. Unfortunately, pediatric patients are more at risk to viral infections due to their lower immunologic memory, and often pay the greatest toll regarding emerging and re-emerging viral threats.

From a clinical standpoint, it is important that physicians are kept abreast on recent achievements in the field of virology and that clinical virologists keep updating the panel of diagnostic assays in order to provide precise answers to ever changing clinical questions. On-site, national and international multidisciplinary networking is also mandatory to confront these rapidly evolving epidemiologic challenges.

Conflict of interest

The authors declare no conflict of interest.

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