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ROTAVIRUSUPDATING

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ABSTRACT
Rotavirus is the principal pathogen involved in severe diarrhea in infants and young children all over the world. All children are infected before two years old, even in developed countries with good hygiene conditions.The generalization of vaccination might significantly reduce the severe forms and therefore will reduce the number of deaths and complications leading to hospitalization.

Keywords : viral gastroenteritis, rotavirus, vaccination

INTRODUCTION

Rotavirus is the most common pathogen of diarrhea in children under five years. This is the pathogen causing the most severe diarrhea, leading to 440 000 to 600 000 deaths per year of children under five in the world, mainly in developing countries with 82% of deaths (1)

MATERIALS AND METHOD

DISCOVERY

In 1963, Adams and Kraft observed by electron microscopy viral particles at the mouse intestinal epithelium infected (2). During the same year, Malherbe and Marwin isolated in monkey a virus of 70nmdiameterdesignated SA11 virus (simian agent 11) (3). Later, similar morphology of viruses have been discovered in cattle, wheel-shaped they were named rotavirus (4, 5)

CLASSIFICATION

Rotavirus (RV) belong to the family Reoviridae, it constitute the genus Rotavirus. There are 7 groups A to G. Only the groups A (above), B and C are involved in human and animal infections. (6)

VIROLOGICAL CHARACTER

• Morphology

RV have a characteristic morphology, wheel-shaped hence their name inspired from the Latin word (Rota), which makes them easily recognizable by electron microscopy after negative staining (see Figure 1). (6)

RV are non-enveloped viruses (have extreme resistance in outdoor environments), the viral particle has a 70 nm diameter and the capsid has an icosahedral symmetry.

• The genome

RV are double stranded RNA viruses segmented into 11 segments. (See Figure 2) (6)

• Proteins and antigenic characters

The 11 segments of the genome encodes 12 proteins

o Six structural proteins, VP1 to VP7, are organized into 3 layers surrounding the genome. (7)

o six non-structural proteins - NSP1 to NSP6 - occur during the reproductive cycle, they are not present in the mature virus. NSP4 have a important role in the mechanism of the diarrhea.

GENETIC AND ANTIGENIC VARIABILITY

RV has a very high genetic and antigenic diversity because several mechanisms: (6)

• Genetic arrangements are common but have little impact on the epidemiology.

• Mutations can lead to genetic derivative responsible to emergence of escape mutants even epidemic strains.

• reassortment between human genomes and between genomes of different species. They are responsible for emergence of new human genotypes such as G9 rotavirus. (6)

PATHOPHYSIOLOGY

o diarrhea Mechanism

Rotaviruses infect enterocytes of the small intestine and cause diarrhea by a complex mechanism and probably multifactorial associating malabsorption and secretory component. (8) A viral infection is caused by the virus itself and NSP4 protein responsible, directly or through a messenger, for activation of the enteric nervous system (ENS) and an increase of intracellular calcium [Ca2 +] causing a succession of events responsible to a leakage of chlorine, disruption of the architecture of the cell and its lysis.

o osmotic diarrhea with malabsorption (8)

Destruction of the tips of the villi enterocytes replaced by immature crypt cells and villus absorptive functions are altered. enterocytesVilli atrophy and die, the lamina propria (LP) is infiltrated by mononuclear cells.

- Functional Impairment of digestion:

– Decrease in enzyme activity (dissaccharidase, lactase, maltase and sucrase-isomaltase) in the mucosa and nutrients fermentation leading to increased intraluminal osmotic pressure.

– Decrease activity of transport systems, including co-sodium-glucose and sodium-leucine transporters (SGLT1), which could be directly linked to the virus and / or its NSP4 protein. This results in a lack of nutrient digestion and a reduction of absorption responsible of osmotic diarrhea.

- The virus and NSP4 protein, directly or through an increase of intracellular calcium, disrupt cellular architecture by acting on cytoskeletal proteins tight junctions. The result is an increase in the transepithelial permeability to macromolecules.
- Villi ischemia due to vasoactive substance produced during infection.

o secretory diarrhea

- rotavirus enterotoxin NSP4 induces an increase of intracellular calcium. One of results is the opening of a calcium-chlorine dependent channel (different from CFTR) responsible for a leak of Cl ions and water.
- Induction of secretion by the NIS. The origin of the NIS activation could be mediators released myofibroblasts and inflammatory cells during infection and / or secretion of peptides and amines from paracrine cells. (8, 9)

MOLECULAR EPIDEMIOLOGY:

The Characterization of G and P genotypes rotavirus strains showed that overall95% of the strains are G1 to G4 types (10). The genotypes of the most common strains are: G1P [8], G3P [8], G4P [8], G2P [4] (10). The virus G1P [8] are the most

frequent (representing 50 to 80% of isolates), followed by viruses G2P [4] and G4P [8]. The virus G3P [8] are rare in general. The frequency of these types may vary from year to year or during the same epidemic season depending on the Geographic location(10).

However, the G1-G4 rotaviruses are not the only ones to circulate in humans.

Many studies have characterized at least 19 types G and 27 P types (10) anda large number of combinations (10). These G-type strains and unusual P aremainly found in developing countries, in Africa, India, Bangladesh, Brazil (11).

It is also in these countries that mixed infections are the most common, fostering the emergence of new strains by genetic reassortment. Among these rare reassortant some may emerge as the RV types G9 and G12 (12).

At Morocco, a molecular epidemiological study of 138 samples of positive stools for rotavirus made by the National Institute of Hygiene showed that 30.6% of samples were G1 [P8], 26% were G9 [P8] 7 5% were G2 [P6], 3.7% were G1 [P6], and 0.7% were G2 [P8]. (13)

TREATMENT

There is no specific treatment. Support is rehydration conduct and monitored according to the clinical condition. Oral hydration is usually sufficient. It uses oral rehydration salts (ORS), marketed as reconstituted powder, whose composed is base on the principle of coupled Sodium-Glucose absorption. ORS should be given in small divided amounts refreshes (about 60 ml every 20-30 min), systematically without waiting for the request (the baby does not know the feeling of thirst). Breastfeeding should not be suspended. ORS should not be used alone over 24, and an early nutrition is necessary. Intravenous rehydration is indicated in cases of severe clinical dehydration (> 10%) or failure of oral treatment causing in particular by vomiting.

The indication of antidiarrheal is limited. (14)

PREVENTION:

Rotavirus surface antigens induce protective immunity against the Severe diarrhea and the knowledge of thevirus structure is necessary for the development of an effective vaccine which research lasted more than 20 years because some imperatives:

- Ensure protection since first months of life, a time when the immune response is not optimal;
- To be nonpathogenic while virulence factors are poorly understood
- Establish a protective local immunity, mainly the fact of live vaccines that have the risk of re-assort with wild virus;
- Cover majority G types who vary geographically (14)

The first rotavirus vaccine (Rotashield, Wyeth Lederle-) was introduced in the US in 1998. Less than a year later, when the vaccine was administered to approximately one million children, Rotashield has been implicated in the occurrence of acute intestinal intussusception and marketing stopped (15).

The second rotavirus vaccine developed is monovalent vaccine Rotarix® (GSK laboratory), is composed of a human strain G1P [8] (or serotype G1P1A). It provides effective protection against the type of RV G1 to G4P but it would be less effectiveagainst genotype strains G2P [4].

And now the pentavalent vaccine, marketed under the name Rotateq® (Merck and Sanofi Pasteur-MSD) includes five human and bovine reassortants (4 types G and one type P). In bovine context (BRV G6P7), this vaccine consists of a mixture of five reassortants expressing the outer layer proteinsof the capsid of human rotavirus type G1, G2, G3, G4 and P1A [8]. The presence of the VP4 gene is one factor for better protection (15).

CONCLUSION

Rotavirus causes 25% of deaths from diarrhea, or 440 000 to 600 000 deaths per year, 82% in developing countries. In developed countries, infection is less severe, estimated between 20 and 40 deaths per year in the United States. (1)

Rotavirus causes a winter outbreak of major socio-economic costs, responsible for 50 to 60% of pediatric hospitalizations for acute diarrhea (1). The spread of rotavirus vaccination is expected to significantly reduce severe formsand consequently the number of deaths and complications cause hospitalizations.

In Morocco we must congratulate the introduction by the public health ministry the monovalent vaccine Rotarix in National Immunization Program (NIP) since January 2010 and it should be noted the importance of continuing the epidemiological surveillance of rotavirus strains.

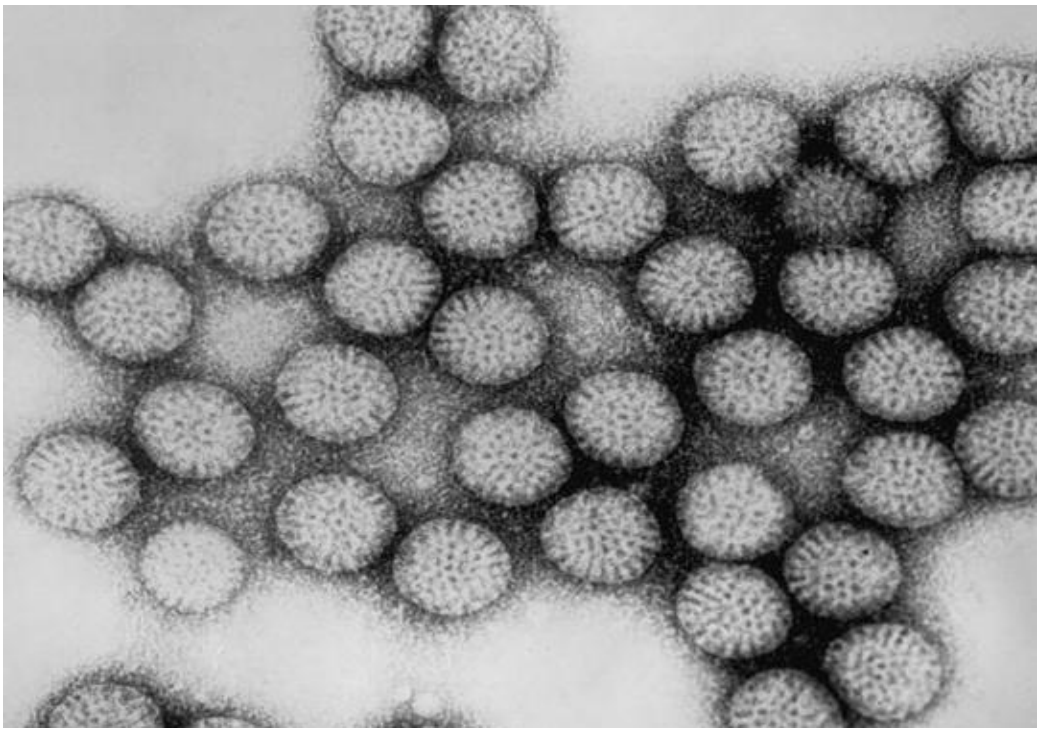

Figure1 : Rotavirus particles aspect observed by electron microscopy after negative staining (6)

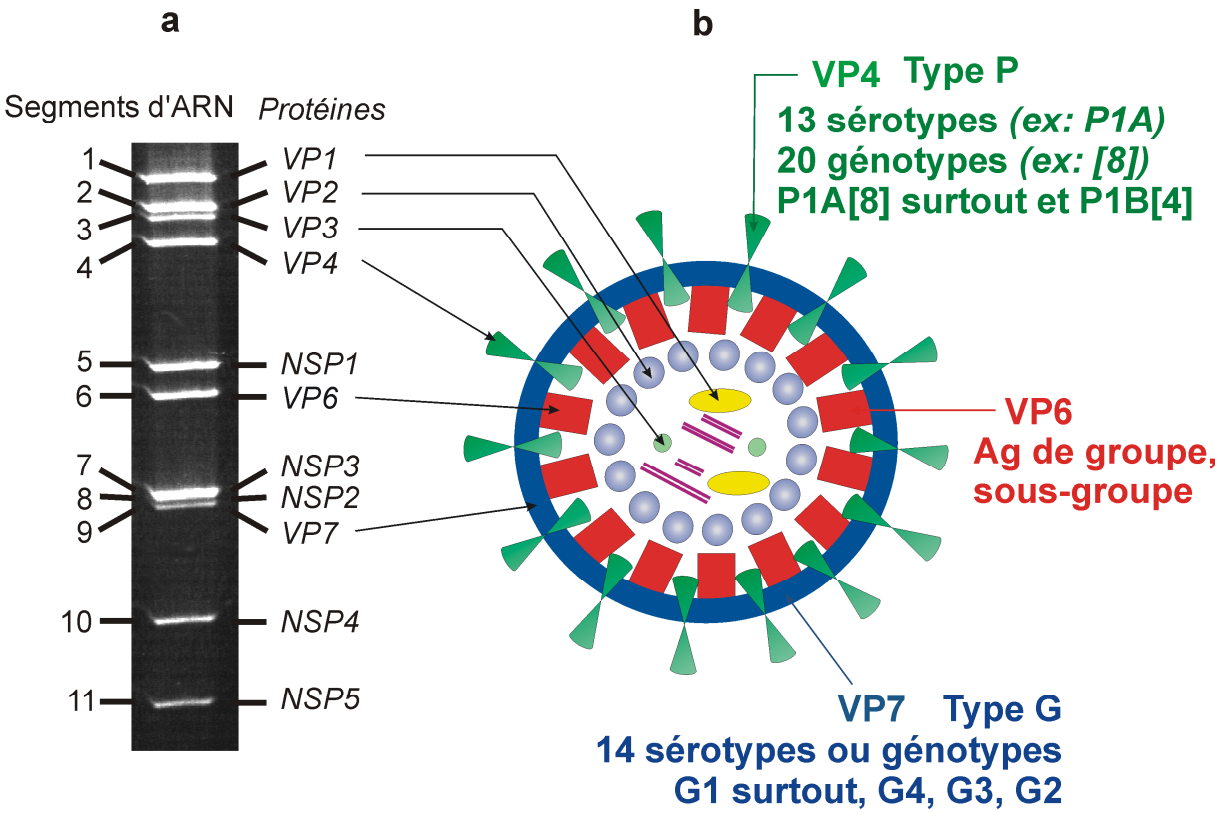

Figure 2 :*Rotavirus Structure: (a) 11 segments of double stranded RNA are separated according to their molecular weight on polyacrylamide gel. The proteins corresponding to these segments are indicated on the right. (b) Schematic diagram of the viral particle. The most common serotypes and G and P genotypes are indicated.(6)*

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