Review article

Measles in children: a re-emergence of the vaccine-preventable disease

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ABSTRACT

Despite the availability of a safe and effective vaccine, measles remains an endemic in many countries and is the main cause of morbidity and mortality among young children. Therefore, the main objective of this study was to describe the most important aspects of measles that allow clinicians to identify suspected cases for timely diagnosis and treatment, which are essential to avoid inappropriate interventions and prevent complications. The measles virus is highly contagious, is transmitted through fomites and respiratory secretions, and remains active in the environment or on surfaces for several hours. Diagnosing measles can be difficult because most clinicians are unfamiliar as there have been few confirmed cases in recent years. Taking a complete medical history, while considering the clinical phases of measles, and a thorough physical examination can help guide the diagnosis, as the main characteristics of measles (fever and rash) can be seen in both infectious and non-infectious diseases. Treatment consists of three fundamental aspects: supportive care (management of fever and hydration), identification and treatment of associated complications, and prevention of disease spread through patient and family group education. It is important to ensure compliance with immunization policies and strategies globally to control the re-emergence of measles and increase in the burden of disease caused by the measles virus.

Keywords: Measles; children; re-emergence; koplik spots; immunosuppression; vitamin A deficiency; vaccine; immunization policies.

INTRODUCTION

Despite the availability of a safe and effective vaccine against measles, the disease remains endemic in many countries and is the main cause of morbidity and mortality among young children (1, 2). Measles has received special attention in children due to the high mortality rates attributed to complications that occur in up to 40% of cases (3-7). Particularly, mortality can be up to 25% in children with malnutrition, immunosuppression, or vitamin A deficiency (VAD) (3, 4, 8-10). There is a broad spectrum of associated complications as they affect different systems; however, pneumonia is the leading cause of death (11-14). Supportive care, early diagnosis, and immediate treatment help in preventing the spread of the measles virus (MV).

In Kyrgyzstan, the number of patients with measles has been increasing since 2018. According to the Republican Center for Immuno-prophylaxis, the Ministry of Health, Kyrgyzstan, 2,345 cases of measles were reported in 2019. Among them, 45.6% were in children under the age of 1 year who were not vaccinated due to their age. An analysis of the vaccination statuses revealed that 2,114 patients (children and adults) were unvaccinated, whereas only 231 (9.9%) of them were vaccinated against measles (15).

The objective of this study was to describe the most important aspects of measles that allow clinicians to identify suspected cases for timely diagnosis and treatment, which are essential to avoid inappropriate interventions and prevent complications.

Pathophysiology

The MV is a single-stranded, unfragmented RNA virus that includes about 16,000 nucleotides and encodes eight proteins. It belongs to the Morbillivirus genus of the Paramyxoviridae family. It is highly contagious, is transmitted through fomites and respiratory secretions, and remains active in the environment or on surfaces for several hours (16-20).

The MV initiates its multiplication at the level of the respiratory epithelium and the mononuclear phagocyte system, mainly affecting lymphocytes, dendritic cells, and alveolar macrophages; this favors viral amplification that triggers an acute viremia phase (6, 16, 18, 21). Initially, there is local replication and spread in the lymphatic tissues (3, 6, 18). Subsequently, the virus spreads through the...
bloodstream and invades the epithelial and endothelial cells of different organs (spleen, liver, brain, skin, lymph nodes, lungs, and kidneys), where it increases its multiplication rate and the maximum viremia level is achieved, where the MV can be identified in peripheral blood cells (T lymphocytes, B lymphocytes, and monocytes) (10, 21). In lungs, the MV damages the apical surface of the epithelial cells or is eliminated through the damaged epithelium, which facilitates respiratory transmission to susceptible hosts (6). On the other hand, it generates a quantitative and functional negative effect on the innate and adaptive immune response that can be associated with transient lymphopenia, probably due to the redistribution of lymphocytes from the peripheral blood to the lymphatic tissues. In turn, a decrease in the proliferation of lymphocytes and alterations in the response and functionality of dendritic cells causes transient immunosuppression that begins before the typical clinical symptoms are observed. The increase in plasma concentrations of IL-10 in children with measles could emphasize immune suppression (22-24).

The period of viremia disappears between the second and third week after the pathophysiological process begins; however, the viral RNA remains in lymphoid organs for 4-6 months after infection (3, 6, 18). After an episode of measles, the initial plasma concentration of CD8+ T lymphocytes is recovered 15 days after the end of the rash phase, that of CD4+ lymphocytes after 30 days, and that of B lymphocytes after 90 days, all of which predispose the patient to greater susceptibility to secondary viral or bacterial infections, mainly six to eight weeks after the measles episode (3, 18, 23, 24). The MV can erase immune memory in infected individuals, impairing the body's ability to fight other diseases that the body is already immune to (25, 26).

Clinical symptoms and complications

Measles can be divided into four phases: 1) the incubation phase, 2) the prodromal (catarrhal) phase, 3) the rash phase, and 4) the recovery phase (3, 4, 8, 11, 16). The incubation phase varies from 7–21 days. Usually, most patients may be asymptomatic or may present subtle signs (3, 8, 10, 11). Then, the prodromal phase begins, in which symptoms such as fever, malaise, cough, and coryza are classically described, that is noticeable 2–4 days prior to the appearance of the rash (8, 16). Koplik spots are the bluish-white spots present on the erythematous base of the buccal mucosa and are considered a diagnostic feature of measles. They usually occur one day before the onset of rash and disappear before complete resolution of the rash (3, 4, 8, 9, 11, 16, 17, 27).

The rash phase is characterized by the appearance of a confluent maculopapular rash that typically extends in the cephalo-caudal direction, which gradually affects the lower limbs and tends to spare the soles and palms. The duration varies from 3-7 days, where disappearance of the rash occurs in an order that is like the chronological appearance (3, 8, 16). Finally, in the recovery phase, most patients have an immune response capable of eradicating the infectious process (11). In this stage, the immune system creates memory mechanisms and builds permanent immunity against the MV (6).

In general, complications occur in 30-40% of cases, mainly in infants, elderly people, pregnant women, immunocompromised or malnourished patients, and children with VAD. The main complications are acute otitis media, pneumonia, encephalitis, keratoconjunctivitis, loss of vision, Dawson disease, and acute disseminated encephalomyelitis (Table 1) (8, 9, 11-14).

Table 1. Complications by organ systems associated with the measles virus (3, 4, 16, 18).

<table>
<thead>
<tr>
<th>Complications by organ systems</th>
<th>Disease</th>
<th>Frequency (case per patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Pneumonia</td>
<td>1/20</td>
</tr>
<tr>
<td></td>
<td>Acute otitis media</td>
<td>1/14</td>
</tr>
<tr>
<td></td>
<td>Laryngotracheobronchitis (Croup)</td>
<td>1/11</td>
</tr>
<tr>
<td></td>
<td>Other (Mediastinal emphysema, Mastoiditis, Pneumothorax)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea</td>
<td>1/12</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Primary measles encephalitis</td>
<td>1-3/1,000</td>
</tr>
<tr>
<td></td>
<td>Subacute sclerosing panencephalitis</td>
<td>4-11/100,000</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>6-7/1,000</td>
</tr>
<tr>
<td>Ocular</td>
<td>Keratoconjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Low birth weight, stillbirth, preterm labour, miscarriage</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis

Diagnosing measles can be difficult because most clinicians are unfamiliar as there have been few confirmed cases in recent years. Taking a complete medical history, while considering the clinical phases of measles, and a thorough physical examination can help guide the diagnosis (3), as the main characteristics of measles (fever and rash) can be seen in both infectious and non-infectious diseases (rubella, roseola, mononucleosis, Kawasaki disease, adenovirus infection, mycoplasmal infection, dengue, Zika, and chikungunya). However, to prevent MV transmission, early virological confirmation is important along with the isolation of cases and quarantining of contacts who have had inadequate vaccination schedules (3, 8, 10).

Serological tests, culture, and polymerase chain reaction are the laboratory tests used for diagnosis (4).
It is technically difficult to isolate the virus from samples collected from nasopharyngeal and conjunctival secretions, blood, and urine; therefore, serological tests for specific IgM antibodies for MV are more widely used (3, 10, 11), which are 100% sensitive when performed 2–3 days after rash onset (11). Specific IgM antibodies are detectable in 75% of patients within the first 72 hours of rash onset; in 100% of cases, specific IgM antibodies against the MV can be detected after the fourth day of infection at the beginning of the eruptive phase (3, 4). Despite the positive aspects of serological tests, real-time polymerase chain reaction is the diagnostic test of choice19 that should be employed in suspected patients (3, 10).

Treatment

Treatment consists of three fundamental aspects: supportive care (management of fever and hydration), identification and treatment of associated complications and prevention of disease spread through patient and family group education (3, 4, 10).

Patients with measles should be in airborne isolation (high-efficiency N95 mask) for four days before and after the onset of rash in case of normal hosts; in immunocompromised patients, the duration should be extended as this is the main period of contagion (3, 11, 28). In turn, because low vitamin A levels are associated with higher rates of complications and increased mortality, the World Health Organization, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention recommend treatment with vitamin A in all patients with acute measles as this is beneficial in reducing morbidity and mortality (3, 4, 9, 18, 29). The recommended dose for children aged ≥1 year is 2,00,000 IU for two consecutive days; in children from to 6-12 months, 100,000 IU for two consecutive days; and, for those <6 months, 50,000 IU for two consecutive days. A third dose is recommended in children with clinical evidence of VAD 2–4 weeks later (3, 4).

Currently, there is no specific antiviral therapy against measles (3). Antibiotics are not prescribed until there is clinical evidence of a bacterial infection due to associated complications (pneumonia or acute otitis media) (3, 18).

Prevention

For over 50 years, measles has been a vaccine-preventable disease. However, it is necessary to ensure population vaccination coverage to 93–95%, which should improve the timely delivery of the vaccine, to stop the endemic transmission and eradicate measles (4). Additionally, governments need to implement more stringent policies for complete vaccination in the population to prevent the re-emergence of measles worldwide (3, 4).

The current vaccination schedule has proven effective. Thus, the administration of a dose at 12 months causes 95% of children to develop immunity against MV; after the second dose, this increased to 99%. The World Health Organization recommends that the first dose be administered from 9–12 months according to the transmission rate of the country and the second dose from 4–6 years of life (3, 4). Despite the greater efficacy, there are anti-vaccine communities and movements that reject vaccines, mainly due to false beliefs, moral or philosophical reasons, or religious positions, and this has led to a resurgence of reported cases worldwide.

Table 2 lists some of the side effects attributable to the vaccine that are generally mild (8). In cases where measles infection could not be prevented, early notification should be provided in case of clinical suspicion; in turn, the patient should be isolated to prevent spread, increase in the number of cases, and the development of an epidemiological outbreak (3, 11, 29).

<table>
<thead>
<tr>
<th>Mild side effects</th>
<th>Severe side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (5-15%)**</td>
<td>Thrombocytopenia &lt; 1 cases/30,000 doses</td>
<td>Severe allergic reaction to any component of the vaccine</td>
</tr>
<tr>
<td>Rash (5%)</td>
<td>Severe allergic reaction or anaphylaxis &lt; 1 case/1,000,000 doses</td>
<td>Previous allergic reaction to neomycin</td>
</tr>
<tr>
<td>Arthralgia (≥ 25%)*</td>
<td>Encephalitis: 0.22/1,000,000 doses</td>
<td>Pregnancy (Avoid pregnancy for four weeks after the administration of the vaccine)</td>
</tr>
<tr>
<td>Lymphadenopathy (5%)</td>
<td></td>
<td>Immune deficiency</td>
</tr>
<tr>
<td>Febrile seizures (0.3-0.8%)</td>
<td></td>
<td>Personal and family history of seizures for MMR vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderately or severely ill patients</td>
</tr>
</tbody>
</table>

*Occurs from 5-12 days after vaccination.
**More common in adolescents and adult women without prior immunization.
In some cases, the seroconversion of the vaccine is affected, such as in blood transfusion and immunoglobulin administrations, and this can affect its immunogenicity. Therefore, it is recommended that vaccination be delayed from 3 to 11 months after blood transfusion or be administered two or more weeks in advance before receiving a transfusion (30). Other contraindications to the vaccine include a history of neomycin contact allergy, pregnancy, and immunosuppression (3, 8, 16, 28).

It is important to ensure compliance with immunization policies and strategies globally to control the re-emergence of measles and increase in the burden of disease caused by the MV.

CONCLUSION

It is important to ensure compliance with immunization policies and strategies globally to control the re-emergence of measles and increase in the burden of disease caused by the MV. The multiple outbreaks observed in different parts of the world where measles is no longer endemic are very alarming and are likely from poor vaccine coverage. It’s important to increase awareness about measles and strengthening vaccine advocacy are imperative in order to prevent it from re-establishing itself as an endemic disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Last accessed on 08 January 2022.