

MEASLES INDUCED DEATH IN EASTERN EUROPE

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Summary. The infectious disease of measles is becoming a rarity in the member states of the European Union. After the implementation of the mandatory immunization calendar, cases of measles among children rarely encounter while those that have been registered usually pass lightly and without any significant complications. We present two cases of a measles-type infection with a fatal outcome for two children – 4 and 11 years of age respectively – who had not been immunized by the time of the event and who developed an unfolding clinical picture with the respective complications. In a number of countries in the European Union (as well as within some ethnical groups, the Roma population included), standard-type vaccinations may appear to be problematic. The most frequently encountered complications, resulting from such “blunders”, are pneumonia and encephalitis but controlling the clinical symptoms is not always possible because of: 1) late medical intervention due to the poor knowledge ability of the respective ethnical group (overdue contact with the specialized medical personnel), as well as 2) the superposed bacterial infections which unmask the initial diagnosis. Obtaining a clear picture of the symptoms in such patients is difficult. In the rare cases, when the therapy is rewarded with some success, patients remain partial or permanent invalids because of the irreversible damage to the brain and/or the functions of the lungs.

Key words: measles, immunization, pneumonia, lethal outcome

INTRODUCTION

The measles infection is a highly contagious disease which manifests with a catarrhal syndrome and characteristic rushes [1]. After the implementation of the mandatory vaccination, no large scale epidemics have been observed [2]. In spite of this, during the early childhood years and in the case of a „breakthrough“ in the immunizations (due to a mistake when administered or when refused), the development of this infectious disease becomes possible in parallel to pneumonia complications, effects on the central nervous system of the measles-type meningitis, encephalitis, meningoencephalitis, pancreatitis, etc. [1-3].

According to a 2012/2013 Lancet publication of a global mortality survey covering 187 countries, during the period 1980 – 2010 the measles-related death rate has fallen considerably: from 9 in 1990 to 1.7 per 100 000 in the year 2010 [4]. It may be of interest to note, however, that between 1 and 6% of the total post-natal infant mortality rate (aged 28 to 364 days) is due to this particular disease [4].

We hereby present two cases with a fatal outcome for the children – non-immunized patients of Roma origin – suffering from a confirmed measles infection with subsequently developing complications.

CASE 1

A child aged four is hospitalized in a generally critical state. About a week earlier it had been in contact with a patient suffering from measles. No strict immunizations were made and no immunization passport was made available. According to the mother and the accompanying medical documentation, the child had been febrile for four days with a temperature reaching 39°C, accompanied by cough and conjunctivitis. Initially the patient was registered at the children's ward with X-ray data revealing the presence of pneumonia in both lungs. Two days after the first hospitalization a facial rash appeared as well as vomiting with the presence of blood matter. Because of the aggravation of the established acidosis and the additionally deteriorating laboratory and vital indicators the child was urgently transferred to the university's Intensive Medical and Reanimation clinic.

Medical history and status: After the hospitalization a measles-type of rash was observed on the face and trunk, Filatov-Koplik spots on the buccal mucosa, enlarged surface lymph nodes on the neck with micropoliadenia. Weakened breathing was also established together with varying crepitations and a frequency of 60/min., tachycardia of up to 220 beats per min, 70/40 mm Hg blood pressure, slightly accelerated peristaltics, enlarged liver to 2.5 cm below the rib arc but no enlargement of the spleen.

The neurological status demonstrated increased muscle tone, intensified reflex activity without the presence of meningoradicular irritation.

Laboratory investigations: Haemoglobin – 77.8 g/l; erythrocyte count – $1.9 \times 10^{12}/l$; haematocrit 0.30; leucocytes – $25.9 \times 10^9/l$; thrombocytes – $238 \times 10^9/l$;

blood glucose level – 7.61 mmol/l; creatinine – 38 μ mol/l, urea – 1.59 mmol/l; bilirubin – 3.2 μ mol/l; ALAT – 42.2 U/l; ASAT – 69.6 U/l (Table 1). Serology for measles revealed positive IgM – ELISA.

Table 1. The patient's laboratory indicators

Indicators	Case 1	Case 2
Hb 120-170 g/L	77.8	132
Er 4.3-5.7 x10 ¹²	1.9 x 10 ¹²	5.1 x 10 ¹²
Hct 0.39-0.49	0.30	0.40
Leu 3.5-10.5 x10 ⁹	25.9 x 10 ⁹	15.1 x 10 ⁹
Plt 150-350 x10 ⁹	238 x 10 ⁹	128 x 10 ⁹
Glucose 4.2-6.4 mmol/L	7.61	7.48
Creatinine 40-140 μ mol/L	38	77.9
Urea 1.7-8.3 mmol/L	1.59	5.61
Direct bilirubin 0.8-8.5 mmol/L	3.2	5.5
ALAT 41 U/L max	42.2	155.1
ASAT 41 U/L max	69.6	27.7

Thoracic X-ray exam was characteristic of bilateral pneumonia.

The patient's therapy included intravenous glucose 5% 500 ml/24, sulperason (cephoperazone & sulbactam) 2 x 150 mg i.v.; methylprednisolone (Urbason) 2 x 10 ml; ambroxol hydrochloride (Flavamed) 3 x 1 ml, oxygen therapy with a mask and intravenous IgG infusion.

Eleven days after hospitalization the child's laboratory and vital indicators continued to deteriorate in spite of the therapy. A cardiac arrest was followed by an intensive but futile reanimation ending in a lethal outcome.

Autopsy and histological findings

During the autopsy a number of pathological deformations were found. The lungs were considerably enlarged, diffusely compacted and heavy. Their sectional surface was dark purple in colour with yellowish blots at certain locations. The tissue was uniform, absolutely airless and when pressed prone to leaking insignificant small quantities of a gray to rose colored liquid. The spleen was also slightly enlarged, somewhat compacted and dark red in color. In the area of the neck, the mediastinum and the mesenterium singular lymph nodes were found with a diameter of 2-3 mm with a soft, elastic consistency and a homogeneous grey to rose coloured sectional surface.

A diffuse haemorrhagic-desquamative bronchopneumonia in the stage of initial organization was found histologically together with a stasis; a heavy swelling and dot-shaped haemorrhages in the frontoparietal areas of the brain; catharral tracheitis was also evident (Fig.1). The remaining organs showed circulatory and degenerative deformations to varying degrees and with no significance for the basic disease. The developed heavy intoxication on the background of the bilateral hemorrhagic-desquamative bronchial pneumonia and measles infection was the immediate cause of death.

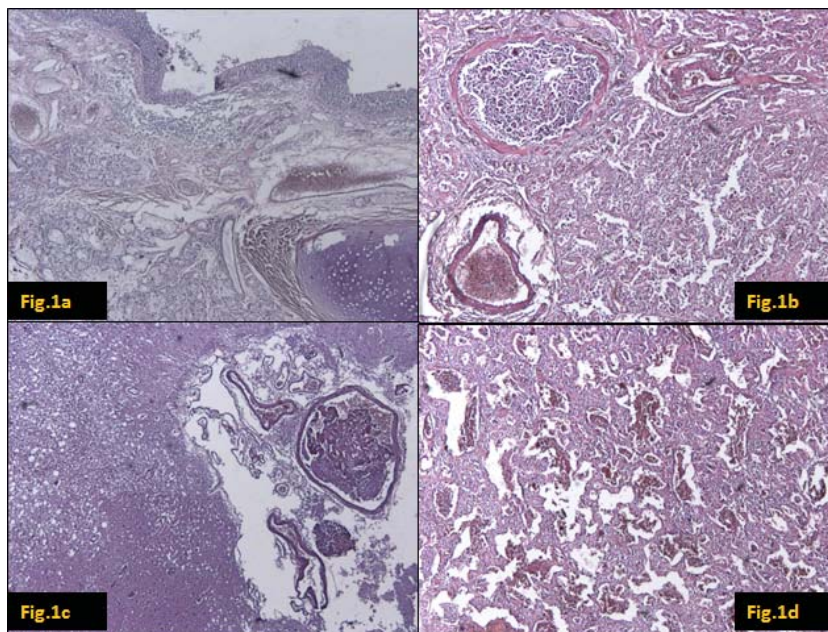


Fig. 1. Histological findings: a) Catarrhal tracheitis; b) diffuse suppuratory haemorrhagic bronchopneumonia organized in deposits; necrotic endobronchitis and bronchiolitis with an expressed squamous cell metaplasia; c) stasis, large swelling; d) diffuse haemorrhagic-desquamative bronchopneumonia in the stage of initial organization

CASE 2

An eleven-year-old boy was initially hospitalized at the Infectious Diseases ward of a municipal hospital with a toxicoinfectious syndrome, sore throat, running eyes and rashes on face and body. Because of the deteriorating overall condition and a progressing respiratory insufficiency the patient was transferred to the university's Intensive Medical and Reanimation clinic.

Medical history and status: The child was registered with a temperature of 38° C, muscle pains, pains in the joints and in the throat. Two days after the appearance of the disease a generalized rash was found on the face and body plus watery eyes. The examination revealed a poor general health status, febrility and perioral cyanosis. The child

had tachypnea – 60/min, acute vesicular bilateral breathing with small moist crepitations. Rhythmic cardiac activity was established with a pulse of 120/min. Abdomen was soft, respiratorily mobile, with a 2 cm liver edge and spleen at 1 cm under the rib arc. A confluent maculopapulous facial rash was observed on the body and the limbs and also periauricularly, as well as enanthema of the palatal arcs and the tonsils with no signs of Filatov-Koplik spots. No data was available on whether the patient had contacted anyone with measles but a registered immunization in the immunization passport conforming to the immunization calendar was lacking (a mandatory immunization should be performed at the age of 13 months – see Table 2).

Table 2. An excerpt from the immunization calendar of the Republic of Bulgaria/Transitional and conclusive regulations, § 13 of the Ordinance for the amendments and supplements to Regulation № 15 on the immunizations in the Republic of Bulgaria (State Gazette, ed.45/2005), published in the SG, ed. 57/24.07.2009

Age	Immunization against	Vaccine	Administration
Thirteen months	Immunization against measles, parotitis and rubeola	Triple vaccine against measles, parotitis and rubeola	Hypodermic or muscular, 0,5 mg
Twelve years	Re-immunization against measles, parotitis and rubeola	Triple vaccine against measles, parotitis and rubeola	Hypodermic or muscular, 0,5 mg

Laboratory investigations: Haemoglobin – 132 g/l; Erythrocyte count – $5.1 \times 10^{12}/l$; haematocrit 0.40; leucocytes – $15.1 \times 10^9/l$; thrombocytes – $128 \times 10^9/l$; blood glucose level – 7.48 mmol/l; creatinine – 77.9 $\mu\text{mol/l}$, urea – 5.61 mmol/l; bilirubin – 5.5 $\mu\text{mol/l}$; ALAT – 27.7 U/l; ASAT – 155.1 U/l /Table 1/. Serology for measles was positive for IgM.

Thoracic X-ray exam was characteristic of bilateral pneumonia (Fig. 2a).

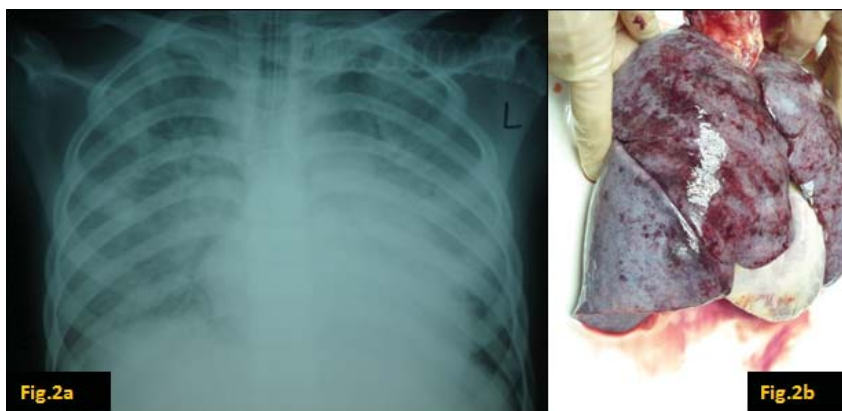


Fig. 2. Macroscopic and X-ray findings: a) Massive bilateral shades of the lung parenchyma; b) bilateral total suppuratory haemorrhagic bronchopneumonia

For eight days the patient was subjected to an intensive conservative treatment with a course of antibiotics, cardiotonics and substitution of intravenous glucose 5% 500 ml/24, potassium chloride 5% 3 x 5 ml; oseltamivir phosphate (Tamiflu) 2 x 75 mg caps; cephepim (Maxipime) 2 x 1.0 g i.v.; amikacin 3 x 100 mg i.v.; digoxin 2 x 0.3 mg i.v., furanthril i.v., as well as oxygen therapy with a mask.

The boy was placed under artificial ventilation due to the ongoing hypoxaemia. On the eighth day after hospitalization the boy exited with cardiogenic shock and respiratory insufficiency.

AUTOPSY AND HISTOLOGICAL FINDINGS

During the brain analysis a large swelling was established, together with fibrine thrombs in the capillaries and venules and a concentration of fresh encephalomalacia. The section and histological examination of the lungs and respiratory tract have found a diffuse suppuratory haemorrhagic bronchopneumonia organized in deposits; necrotic endobronchitis and bronchiolitis with an expressed squamous cell metaplasia; hyalinic membranes, siderophages and deposits of anthracosis (Fig. 1, 2 b). In addition, an interstitial swelling of the myocard accompanied by parenchymal degeneration of the cardiomyocytes was also made evident. In conclusion, the pathomorphological examination has established the main disease to be the bilateral suppuratory haemorrhagic bronchopneumonia entirely covering the parenchyma of the lungs. The heavy intoxication which developed as well as the terminal acute cardiovascular insufficiency demonstrated by profound degenerative and circulatory deformations of the internal organs were the immediate causes of the lethal outcome. The anamnestic data for the generalized maculopapular confluent rash on the body, enanthema of the palatal arcs and tonsils as well as the positive serological results for measles have given us sufficient grounds to accept the measles infection as the major background disease.

DISCUSSION

According to the data submitted by the European Centre for Disease Prevention and Control (ECDC), subsequent to an extended period of absence of the measles disease in Bulgaria, by the end of April 2009 a large epidemic was witnessed with 24 registered lethal cases – mainly of babies, children and adolescents [5]. We present two cases of patients contracting measles followed by complications resulting from the major disease may be viewed as an example of immature immunity and negligence in the process of realizing the mandatory vaccination procedures.

In the last decade several outbreaks of measles have been observed throughout Europe. In Western Europe vaccination rejectionists and loss of interest in the general population were responsible for outbreaks in Germany. Only two of eight German states almost reached the 95% vaccination rate recommended by the WHO for the elimination of measles. In particular adolescents show an insufficient vac-

cination [6]. When we look for particular affected groups in Europe, Sinti and Roma communities, anthroposophic groups, ultra-orthodox Jewish communities and immigrants are at particular risk due to the lack of or to the incompleteness of vaccination [7].

When clarifying the status of patients, and especially children and adolescents with maculopapulous rash and high temperature, the process of establishing the administered vaccinations and their entry in the immunization passports is of major importance. The additional laboratory, image diagnostics and – when possible – serological investigations are a major support to the prompt diagnosis of the disease and the subsequent optimization of the therapeutic schemes. Interstitial pneumonias are often difficult to register auscultatory and this implies that additional X-ray diagnostics have to be performed.

From the point of view of pathophysiology, the basis of all respiratory virus diseases with a toxicoinfectious syndrome stands on the ability of such microorganisms to be “glued” to the cells of the respiratory epithelium with the help of virus haemagglutinins after which, and under the effect of the neuraminidases, the cycle is continued and after penetrating the cell they replicate the virus [8]. On the one hand, all of this is paralleled by profound damages and apoptosis of the effected cells and on the other, by the activation of immunocompetent cells and a number of cell and tissue mediators all of which lead to morphological and pathophysiological deformations in the effected organ. According to Sabella et. al., three out of 1000 patients will die from a measles-type of disease while complications connected to the respiratory and nervous systems, the gastrointestinal tract, etc., are observed with greater frequency [9]. Other than viral tracheitis, pneumonitis and pneumonias the measles disease becomes, quite often, additionally complicated by a secondary bacterial infection of the lungs caused by the *Staphylococcus aureus* or *Streptococcus pneumoniae*.

Still other complications appear in the form of morbillis encephalitis and the sub-acute morbillis panencephalitis where, in the first case, patients develop headaches, convulsions and mental alterations while morphologically, locations of demyelination in the structures of the brain may be found to be caused by a post-infectious autoimmune reaction, the development of which takes different time frames (10, 11). Similar to literary descriptions one of the patients in our presentation had a massive encephalomalacia resulting from an acute inflammation of the brain.

The development of the measles-related complications is, quite often, clinically manifested in children and young people. Chatterjee et al. remark, that mortality rates are higher within the group of infants not older than 1 year and lower within the 1 to 9 year-old children [12].

CONCLUSION

The two cases we have presented revealed the picture of unfolding complications accompanying a measles infection in two children of missing vaccination. In spite of the established diagnosis and therapeutic activities both died suffering

from a toxicoinfectious syndrome and acute respiratory insufficiency. The knowledge about measles within certain ethnical groups is low and the standard vaccination procedures are often being neglected. In addition, the sheer lack of or negligent safekeeping of the immunization passports leads to critically important delays in the application of intensive life-saving therapies. This results in a considerable growth in the number of affected children, who develop secondary bacterial lung infections, meningitis/meningoencephalitis leading eventually to a higher mortality. Improvement of information for risk groups and improved vaccination are necessary.

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