CASE REPORT

Multiple Measles Cases Despite Vaccination in a Paediatric Care Unit

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THE CASE

On the 14th of February, 2018, a young Cyprian girl, who originally returned for a follow-up examination, was admitted to a Hungarian paediatric unit due to new onset fever, cough, lymphadenopathy, swollen eyelids and neutropenia. The following day she developed maculo-papular rash and on the 18th of February she was quarantined. The next day, after confirmation of measles infection by serology and polymerase chain reaction (PCR) she was transferred to a hospital specialized in treatment of infectious diseases. Following her transfer three nurses directly tending her at the ward were diagnosed with measles infection, despite the employer's booster vaccination campaign the previous year.

Nurse A (age 50) was the first to develop symptoms: chills and pain in the extremities on the 27th February. On the 1st March rash appeared on her head, arms and chest, which was itching and spread to the neck and the face the following day. By this time the chills and pain vanished. The serum taken for serology on the 5th proved to be positive for both IgM and IgG anti-measles antibodies, and high-avidity measles IgG antibody was detected. The PCR test of the throat swab specimen was positive for genotype B3. Serological investigation of paired sera (second serum specimen collected on the 14th of March) also confirmed acute measles infection. Nurse B (age 30) developed head- and neck ache on the 2nd March. The following day her skin was itching and rash appeared on her head, arms and chest. She had no fever but a sore throat and Koplik's sign (white-red spots on the buccal mucosa) for three days. Nurse C (age 41) developed fever on the 2nd of March. Later rash appeared on her head and the extremities. In both later cases the sera taken on the 5th were IgM negative and IgG positive for measles. The avidities were high and the PCR tests gave negative results. Serological investigation of paired sera (second sera taken on the 14th) confirmed acute measles infections for both of them. In every case the tests ruled out acute Parvovirus B19 and rubella infections. West Nile virus infection was unlikely in the time of the year. All three nurses were on sick-leave and recovered completely in a short time and they have not infected anyone. The affected unit was quarantined and disinfected. The above listed laboratory results referred to secondary vaccination failure. Details of the laboratory tests are described in Table I.

The workers' vaccination history is the following: Both nurse A and nurse C must have received a single dose of monovalent measles vaccination during infancy. Furthermore, they must have received a booster dose during the vaccination campaigns due to Hungarian epidemics in the 1980-ies (CDC, 1989). However, no written documentation is available. Nurse B is from the age group that received mandatory two doses of measles-mumps-rubella (MMR) vaccination during childhood. All three nurses were found seronegative during the occupational health screening for immunisation in spring 2017. They were all given single booster doses of MMR vaccination in September.

Although Hungary has eradicated measles, it is still a cross-border threat (ECDC, 2019). Minor measles epidemics occurred four times in 2017 and once in 2018 in Hungary due to imported cases from Romania. The sources of two 2017 outbreaks could not be identified (WHO, 2018). One case imported from Ukraine and one from Kazakhstan also initiated Hungarian epidemics in the first quarter of 2019. The database of our laboratory contains the following number of verified measles infections (including sporadic cases): 36 in 2017, 14 in 2018 and 12 in 2019Q1. The initial outbreaks received high publicity and prompted the nurses' employer to check all employees' status of immunisation against measles in 2017. Those who were found seronegative and borderline were given a booster MMR. However, no repeated tests were performed to verify the protective effect of the boosters. Therefore there is no data on whether the workers' serostatuses have converted or not. Our story is completed with antecedent information revealed by the epidemiological investigation: on the 31st of January, 2018 the Cyprian girl was admitted to the same room of the hospital where a Romanian child was treated who was found to be infected.

Table I.

Detailed laboratory results and methods

	Day of sample collection	**March 2017**	**05/03/2018**	**14/03/2018**	**05/03/2018**	**05/03/2018**	**05/03/2018**
Patient	**Test**	**immunisation testing**	**1st blood sample**	**2nd blood sample**	**EDTA**	**Throat Swab**	**Urine**
Nurse A	IgM ELISA	-	positive (R=1.29)	negative (R=0.66)	-	-	-
	IgG ELISA	negative (R=0.44)	positive (R=4.92)	positive (R=5.01)	-	-	-
	IgG Avidity ELISA (1:101) (RAI)	-	(OD>1 200) 104%	-	-	-	-
	IgG Avidity ELISA (1:1601) (RAI)	-	run out	(OD>1 200) 94.6%	-	-	-
	IgG IFA (In-house)*	-	1:40 960 (+/-)	1:20 480 (+/-)	-	-	-

	IgA IFA (In-house)	-	≥1:20 (+)	-	-	-	-
	IgG IFA (MASTA-FLUOR)**	1:10 (+/-), 1:20 (+/---)	-	-	-	-	-
	RT-PCR	-	-	-	negative	positive	negative
Nurse B	IgM ELISA	-	negative (R=0.23)	negative (R=0.21)***	-	-	-
	IgG ELISA	negative (R=0.45)	positive (R=5.06)	positive (R=5.43)	-	-	-
	IgG Avidity ELISA (1:101) (RAI)	-	(OD>1 200) 97%	-	-	-	-
	IgG Avidity ELISA (1:1601) (RAI)	-	(OD>1 200) 87.5%	-	-	-	-
	IgG IFA (In-house)*	-	1:5 120 (+/-)	1:10 240 (+/--)	-	-	-
	IgA IFA (In-house)	-	≥1:20 (++++)	-	-	-	-
	IgG IFA (MASTA-FLUOR)**	1:10 (+/-), 1:20 (+/---)	-	-	-	-	-
	RT-PCR	-	-	-	negative	negative	negative
Nurse C	IgM ELISA	-	negative (R=0.37)	negative (R=0.52)***	-	-	-
	IgG ELISA	negative (R=0.57)	positive (R=4.89)	positive (R=5.3)	-	-	-
	IgG Avidity ELISA (1:101) (RAI)	-	(OD>1 200) 94%	-	-	-	-
	IgG Avidity ELISA (1:1601) (RAI)	-	(OD<1 200) 81.44%	-	-	-	-
	IgG IFA (In-house)*	-	1:640 (+)	1:10 240 (+/-)	-	-	-
	IgA IFA (In-house)	-	≥1:20 (+)	-	-	-	-
	IgG IFA (MASTA-FLUOR)**	1:10 (++/-), 1:20 (+/--)	-	-	-	-	-
	RT-PCR	-	-	-	negative	negative	negative

* Measles-specific IgG antibodies were investigated in paired sera.

** The indirect immunfluorescent test was performed retrospectively in June, 2019.

*** Serological test performed by Anti-Measles Virus Nucleoprotein ELISA IgM kit of EUROIMMUN.
OD: optical density
RAI: relative avidity index in %
R: Ratio (extinction of the patient sample/extinction of the calibrator=Ratio, cut-off=1)

ELISA kits:
Anti-Measles IgM antibody EUROIMMUN (Medizinische Labordiagnostika AG, Germany) /Results were evaluated semiquantitatively.

Anti-Measles IgM antibody Nucleoprotein EUROIMMUN (Medizinische Labordiagnostika AG, Germany) /Results were evaluated semiquantitatively.

Anti-Measles IgG antibody EUROIMMUN (Medizinische Labordiagnostika AG, Germany)/Results were evaluated semiquantitatively.

Anti-Measles IgG antibody avidity EUROIMMUN (Medizinische Labordiagnostika AG, Germany)/ Patient samples were diluted to 1:101 with sample buffer. According to the test instruction the test for relative avidity index determination of samples with extinction values (optical density/OD)>1 200 without urea treatment were repeated with higher sample dilution (1:1601). Further dilution was not tested.

Indirect immunfluorescence assays:
Investigation of the Anti-Measles IgG antibody titers in paired sera was performed using in-house immunofluorescence assay (IFA).

Detection of the Anti-Measles IgA antibodies was performed using in-house immunofluorescence assay (IFA).

Anti-Measles IgG antibody indirect immunfluorescence assay (IFA) MASTAFLUOR (Mast Diagnostica GmbH, Germany) was used for screening of the IgG antibodies in 1:20 dilution and for investigation in 1:10 dilution to detect very low level of IgG antibodies in sera of vaccinated persons to prove previous vaccination.

Results were interpreted by description of the fluorescence intensity according to the following ratings/ categories:
high or moderate fluorescence intensity.: (++++), (+++), (++), (+)
low fluorescence intensity: (++/-), (+/-)
very low fluorescence intensity: (+/--), (+/---)
no fluorescence detected: (-)

Molecular tests:
QIAamp® Viral RNA Mini Kit (QIAGEN, Germany) was used for isolation of measles RNA, and RT-nested PCR (validated by national reference laboratory) for the detection of RNA. The primers used for RT-PCR were amplifying a 400 bp (pos 465–864) product of the N terminal region of the N gene. The primer set used in the reaction is appropriate for virus identification, but not for genotyping. For genetic characterization, primers were used according to the WHO protocol for amplifying the fragment of the 450 nucleotides coding for the carboxyl-terminal of the nucleoprotein gene. These PCR products were sequenced using a 3500 Genetic Analyzer (Applied Biosystems).

A substantial part of global measles infections happens despite appropriate vaccination: in five years 38 677 infections were reported from persons who received two vaccination doses (Patel and Orenstein, 2019). Recent European outbreaks raised the possibility of secondary vaccine failure. Our report is not the first from this sector. In 2014 there were several measles infections with mild symptoms among vaccinated healthcare workers in the Netherlands: the authors calculated 52% effectiveness for 2 doses of measles vaccine (Hahné et al., 2016). However, it is unique to our knowledge to report on boosters that were administered within a year and could not prevent multiple infections in a hospital setting.

There are several explanations that could be considered. It is very unlikely that all three nurses were true non-responders because the avidities in the samples were high and non-responders are estimated to be around 2-5% (CDC, 2015). High-Avidity measles IgG, which reflects matured immunity, can help in confirming previous vaccination among measles infected persons (Sowers et al., 2016). Loss of vaccine effectiveness due to genetic variation of the measles virus is also an unlikely explanation (Bankamp et al., 2011). The booster vaccination could have been hampered by some mistake, like an error in the supply chain. MMR is known to be highly heat sensitive (WHO, 2014). A conclusion of random clustering of persons not responding properly to the vaccination cannot be excluded without comprehensive data on vaccination effectiveness in the entire hospital. Thus the certain determination of the cause would require the testing of every worker who received the booster dose in 2017. All in all, the cases draw attention to the weaknesses of measles vaccines and to the importance of individual serological testing for the effectiveness of vaccination. Contrary to the general population where the goal is to reach the level of herd immunity, in a working environment setting the occupational health practitioner cannot accept partial coverage of the exposed worker population. In the future one might consider testing for effectiveness after booster vaccination and a regular monitoring of the heavily exposed population. As waning immunity can occur and a third MMR vaccine may not be effective in boosting antibodies (Fiebelkorn et al., 2016), the cases raise several questions. Is there a vaccination regime that is able to provide full protection to health care workers? If two doses of vaccine (in childhood) can safely prevent cases with complications, is it justifiable to abandon (the costs and risks of) tests and booster vaccinations and reserve such measures where patient safety and healthcare business continuity are crucial?

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Key Words: measles, health care worker, vaccination failure

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