

Measles in paediatric patients in Poland – a 3-year retrospective single-centre study

Maciej Stępień¹, Martyna Cholewik¹, Magdalena Eksmond¹, Agata Piotrowska¹, Małgorzata Sokołowska¹, Carlo Bieńkowski^{2,3,4}, Maria Pokorska-Śpiewak^{3,4}

¹Student Scientific Circle at the Department of Children's Infectious Diseases, Medical University of Warsaw, Warsaw, Poland

²Doctoral School, Medical University of Warsaw, Warsaw, Poland

³Department of Children's Infectious Diseases, Medical University of Warsaw, Warsaw, Poland

⁴Hospital of Infectious Diseases, Warsaw, Poland

ABSTRACT

Introduction: Measles is a highly contagious viral disease. In recent years, there has been an alarming increase in measles cases in Europe. Most patients were not vaccinated. The aim of this study was to analyse the clinical manifestation of measles in paediatric patients, considering the differences between infants and older children.

Material and methods: This was a retrospective observational study, for which data were collected from the medical records of paediatric patients hospitalised due to measles January 2017 – December 2019. Stratification was based on age. In the younger group (infants), children under 13 months of age were included.

Results: In total 84 children were enrolled in the study, including 26 infants (30.95%) and 58 older children (69.5%). In 67/84 (79.76%) participants no history of measles vaccination was reported. Among those not vaccinated, there were 28/67 (41.79%) children too young for vaccination. Fever and erythema occurred in all patients. The disease was complicated by pneumonia in 39/84 (46.43%) and acute otitis media in 19/84 (22.62%) children. Antibiotics were administered in 45/84 (69.05%) cases, of which 10/58 (17.24%) had 2 or more. The infants had significantly less frequent photophobia ($p = 0.041693$), lymphadenopathy ($p = 0.005229$), hepatomegaly ($p = 0.030619$), and splenomegaly ($p = 0.019469$). Instead, they were significantly more likely to have acute otitis media ($p = 0.020141$).

Conclusions: Measles is a serious disease that most commonly affects unvaccinated children. The most common symptoms include fever and rash. Otitis media and pneumonia were the most common measles complications. The variations in symptoms and complications of measles differ significantly between infants and older children.

KEY WORDS:

measles virus, vaccination, paediatric patients, viral infections.

INTRODUCTION

Measles is a highly infectious, febrile disease caused by a virus of the *Morbivirus* genus. Prior to the introduction of the measles vaccine in the 1960s, measles was the leading cause of mortality and morbidity in children worldwide [1]. The measles is an air-borne disease that, in temperate climates, shows an annual seasonality – epidemics usually occur in late winter and spring [1]. Usually, the infectious period lasts from 4 days before to 4 days after the rash appearance [2]. After an incubation period of 8–12 days, the disease begins with fever, cough, coryza,

and conjunctivitis. Followed by Koplik's patches a day or two before rash appearance. The characteristic erythema is blotchy and appears 2–4 days after the fever onset. It is initially marked on the face and behind the ears and then spreads to the trunk and limbs [1, 3]. The rash persists for 3–7 days and subsides in the same order in which it appeared, while the fever lasts for 2–3 days after onset of the rash, and cough may persist for 10 days [1, 4]. Due to the lack of aetiologic antiviral treatment for the disease, measles management consists of 3 aspects including symptomatic therapy, complications treatment, and further spread prevention of the disease [2]. Symptomatic

ADDRESS FOR CORRESPONDENCE

Dr. Carlo Bieńkowski, Medical University of Warsaw, Warsaw, Poland, e-mail: carlo.bienkowski@gmail.com

therapy includes fever treatment, and prevention or compensation of dehydration, and nutritional deficiencies. Secondary bacterial infections, causing e.g. pneumonia or otitis media, require treatment with antibiotics, while the use of prophylactic antibiotics is not recommended [1]. Serious complications and death are more likely to occur in children under 5 years of age, and in malnourished, and immunocompromised children, especially those with vitamin A deficiency. In children with measles, vitamin A supplementation has been shown to alleviate the symptoms of the disease and reduce the mortality rate [1, 4]. Approximately 30–40% of patients with measles will develop one or more complications. Pneumonia is the most common serious measles complication and accounts for most measles-related deaths in children [4]. It may be caused by the measles virus itself, or by secondary adenoviral infection, herpes simplex virus, or secondary bacterial infection [3]. Measles vaccination was introduced largely to reduce the risk of severe and complicated courses of the disease [1]. The measles vaccine provides 95% protection against the disease and is 92% effective in protecting household members from secondary contacts [2, 3]. Following measles exposure, some vaccinated individuals experience an increase in antibody titres associated with mild symptoms, and they may develop a rash with slight fever or non-specific respiratory symptoms [2, 3]. According to Polish guidelines, vaccination against measles in children is free and mandatory. The first dose of measles, mumps, and rubella vaccine should be administered 13–15 months of age, and the second dose at the sixth year [5]. Measles complications, including pneumonia, chronic neurological conditions, and death, have been significantly reduced after the introduction of measles vaccination in 1975 in Poland [6]. The World Health Organisation (WHO) recommends that the first dose of measles vaccine should be administered to children at 9 months of age in measles endemic areas; however, giving the first dose of vaccine at 12–15 months of age results in a higher proportion of children being protected against measles for longer period. This scheme can only be used in areas where the risk of measles is low [1].

The aim of the study was to analyse the clinical manifestation of measles in paediatric patients, focusing on the differences between infants and older children.

MATERIAL AND METHODS

All paediatric patients hospitalised due to measles January 2017 – December 2019 in the Department of Children's Infectious Diseases, Medical University of Warsaw, Poland, were retrospectively analysed. The diagnosis of measles was based on polymerase chain reaction testing, for which clinical samples were collected immediately after the suspicion of measles. The polymerase chain reaction test was carried out up to the fourth day after the onset of the rash, while on the following days measles

was confirmed by testing IgM antibody levels. Measles infection was defined as fever followed by a rash, together with at least one of the “3 Cs”: cough, coryza, conjunctivitis, and a history of measles exposure (epidemiological chain). A rash that was not blotchy and did not start on the face was qualified as atypical. Children in this study younger than 12 months were defined as too young to be vaccinated. The patients without confirmed diagnosis based on former requirements were excluded from the study. Demographic, clinical, and laboratory data were collected from electronic medical records and analysed. Data included: sex, age, previous immunisation status, exposure to measles, length of hospitalisation, clinical and laboratory parameters, administered treatment, and occurring complications. The study group was divided into 2 subgroups for further analysis. Stratification of study participants was based on the age of the children; those under 13 months of age were allocated to the infant group and the others to the older children group. This division was made because of the inability to vaccinate infants and the presumed worse prognosis in these children.

The Mann-Whitney *U* test was used to compare continuous variables, and the χ^2 or Fisher exact test were used to assess categorical variables. A *p*-value of < 0.05 was considered significant. Statistical analysis was performed with Medcalc ver. 20.009, Ostend, Belgium.

RESULTS

All 84 patients were hospitalised due to measles in Department of Children's Infectious Diseases in Medical University of Warsaw, Poland, January 2017 – December 2019. There were 37 girls and 47 boys. Their median age was 1 year and 11.5 months (interquartile range [IQR]: 11–68.75 months). Median length of hospitalisation was 4 (IQR: 3–5) days. Possible contact with an infected person was reported by 38/84 (45.24%) of patients. The number of children not originating from Poland amounted to 15/84 (17.86%), most of them were from Ukraine – 9/15 (60%). No history of measles vaccination was indicated by 67/84 (79.76%) patients, while 5/84 (5.95%) of children had received vaccination, including 2 of them who received postexposure prophylaxis. None of the vaccinated children with measles received 2 doses of the vaccine. No vaccination data was available for 12 (14.29%) patients. Of those not vaccinated, there were 28/67 (41.79%) children too young for vaccination. Fever and exanthema occurred in all patients. In 17/84 (20.24%) the exanthema had atypical course and/or location. The exanthema appeared as follows: in 31/84 (36.90%) one day prior to hospital admission, in 15/84 (17.86%) 2 days before admission, and in 15/84 (17.86%) on the day of admission. The median number of days after which it started to disappear was 5 (IQR: 4–6). The median duration of fever was 6 (IQR: 5–7) days, median day of rash appearance and disappearance was 4 (IQR: 2.5–5) days before and 2 (IQR: 2–3) days

after the hospital admission, respectively. The cough occurred in 78/84 (92.86%) of patients, and coryza in 55/84 (65.48%) of them. In 75/84 (89.29%) cases conjunctivitis occurred, and in 33/84 (39.29%) it was accompanied by photophobia. In 56/84 (66.67%) of children Koplik's spots were found. Hepatomegaly was observed in 47/84 (55.95%) patients and splenomegaly in 28/84 (33.33%). Lymphadenopathy was present in 35/84 (41.67%) children. The cervical lymph nodes were enlarged in 14/35 (40%) patients, and in 8/35 (22.86%) the lymph nodes of mandible angle were also swollen. Among those with lymphadenopathy, 5/35 (14.29%) children had generalised lymphadenopathy. At least one abnormality in blood tests (including anaemia, neutrophilia, neutropaenia, lymphocytosis, lymphopaenia, leukocytosis, leukopaenia, thrombocytosis, or thrombocytopenia) was present in 66/84 (78.57%) children. An uncomplicated course of measles occurred in 27/84 (32.14%) children. The incidence of complications of measles is shown in Table 1. Antibiotics were administered in 45/84 (69.05%) patients who developed bacterial complications, of which 2 or more of them were administered in 10/58 cases (17.24%). Most commonly administered antibiotics were cefuroxime in 27/58 (46.55%) cases, amoxicillin in 13/58 (22.41%), and ceftriaxone in 10/58 (17.24%). In 38/84 (45.24%) cases nystatin was administered. In 20/84 (23.81%) patients steroids were administered for laryngitis, and 7/84 (8.33%) were treated with β -2-mimetics (Table 1).

The infants had significantly less frequent photophobia (6/26, 23.08% vs. 27/58, 46.55%, $p = 0.041693$), lymphadenopathy (5/26, 19.23% vs. 30/58, 51.72%, $p = 0.005229$), hepatomegaly (10/26, 38.46% vs. 37/58, 63.79%, $p = 0.030619$), and splenomegaly (4/26, 15.38% vs. 24/58, 41.38%, $p = 0.019469$). Instead, they were significantly more likely to have acute otitis media (10/26, 38.46% vs. 9/58, 15.52%, $p = 0.020141$) (Table 2).

DISCUSSION

Measles is an infectious disease with a marked increase in the number of cases in Poland between 2017 and 2019. In 2017 there were 63, in 2018 – 359, while in 2019 as many as 1502 [7]. The numbers apparently decreased in recent years; however, measles should not be underestimated because it is a disease that may have a severe course and can be followed with multiple complications [7]. In Europe, the problem of a high incidence rate was also evident. The number of cases in this region during consecutive years was 25,863 in 2017, 88,693 in 2018, and 101,280 in 2019 (January – October) [8]. In a study by Ben-Chetrit *et al.* in which 161 participants were hospitalised, as many as 86 (53.4%) were younger than 5 years old. It is worth noting that only 9 patients (5%) were vaccinated according to the full vaccination regimen. Almost all of the children aged 5 years or younger were unvaccinated (98%), whereas less than half

(46%) were less than one year old (therefore they could not be vaccinated according to the routine recommendation of giving the first dose from 12 months of age) [9]. The 2017–2018 measles outbreak in Greece primarily affected the paediatric group. Gianniki *et al.* described 578 children aged 0–16 years, and the median age of measles patients was 36 months. The highest prevalence of measles was found in the 1–5 year age group (43.4%), followed by infants under one year of age (20.3%) [10]. According to Angelo *et al.*, typically the annual number of cases in the WHO European region 2010–2017 ranged from 5000 to 24,000, whereas in 2018 there was the highest number of measles cases in the region, with more than 41,000 cases and 37 deaths reported in the 6 months from January to June, with the highest incidence in children under 5 years of age [11]. Most of children hospitalised due to measles were unvaccinated [12]. In our study, 84 patients were hospitalised, and their median age was 23.5 months. The group of vaccinated children accounted for only 5 patients (5.95%), while of the unvaccinated group, as many as 28 patients (33.33%) were too young to receive the first vaccine dose. In the period January–June 2018, the highest number of measles infections was recorded in Ukraine, i.e. more than 23,000 cases. Between July 2017 and June 2018, the incidence of measles in Ukraine exceeded 600 cases per million people [11]. In our study, 15/84 (17.86%) patients were not originally from Poland, and as many as 9 patients (60%) of those were from Ukraine. Due to the large influx of refugees from Ukraine to neighbouring countries, additional attention should be paid to the increased risk of new measles cases. Despite the low number of reported measles cases in Ukraine in 2020, these results should be interpreted with caution due to the limited non-COVID-19 infectious disease surveillance at the time [13]. Domai *et al.* in a cohort of 5562 hospitalised children with a median age of 11 months, showed that 98% of the children had cough, 81% had coryza, whereas 47% had conjunctivitis [14]. In our study, the children presented with fever (84/84, 100%), cough (78/84, 92.86%), coryza (55/84, 65.48%), and conjunctivitis with photophobia (33/84, 39.29%). Koplik spots do not occur in all measles patients [2]. According to Bentley *et al.*, this symptom occurs in 60–70% of patients infected with measles virus [15]. In our study, as many as 56/84 (66.67%) manifested with this symptom. In the following days, patients begin to develop a maculopapular skin rash that appeared behind the ears and then spread to the face, trunk, and extremities [16]. Next to fever, it is the most common symptom of the disease, occurring in most patients, sometimes in all participating patients [17, 18]. In our study, 100% also manifested with a rash, and in 17/84 (20.24%) it was atypical. According to the Cornelissen *et al.* study, which analysed data on 220 of 289 hospitalisations, the median length of stay was 5 days (range 1–42 days). Hospitalisations of children aged 1–14 years were significantly

TABLE 1. Characteristics of patients hospitalised due to measles January 2017 – December 2019 in the Department of Children's Infectious Diseases in Warsaw

Characteristic	N = 84	Characteristic	N = 84
Demographics and epidemiological background		Laboratory results	
Age in months (IQR)	23.5 (11–68.75)	Enlarged cervical lymph nodes, n (%)	14 (14.67)
Female sex, n (%)	37 (44.04)	Enlarged mandibular lymph nodes, n (%)	8 (9.52)
Possible contact with measles, n (%)	38 (45.24)	Generalised lymphadenopathy, n (%)	5 (5.95)
Non-Polish citizens, n (%)	15 (17.86)	Minimum 1 deflection, n (%)	66 (78.57)
Ukrainian citizens, n (%)	9 (10.71)	Anaemia, n (%)	17 (20.24)
Vaccinations against measles		Neutropaenia, n (%)	9 (10.71)
Vaccinated, n (%)	5 (5.95)	Neutrophilia, n (%)	12 (14.29)
Unvaccinated, n (%)	67 (79.76)	Lymphopaenia, n (%)	27 (32.14)
Too young for vaccination, n (%)	28 (33.33)	Lymphocytosis, n (%)	24 (28.57)
No vaccination data available, n (%)	12 (14.29)	Leukopaenia, n (%)	14 (16.67)
Hospitalisation		Leukocytosis, n (%)	3 (3.57)
Median days of hospitalisation (IQR)	4 (3–5)	Thrombocytopaenia, n (%)	1 (1.19)
Fever		Thrombocytosis, n (%)	9 (10.71)
Presence, n (%)	84 (100.00)	Increased percentage of band cells, n (%)	5 (5.95)
Median duration, in days (IQR)	6 (5–7)	Elevated C-reactive protein level, n (%)	62 (73.81)
Median duration before admission (IQR)	4 (2.5–5)	Median ALAT level (IQR)	22 IU/l (17.5–29.75)
Median duration after admission (IQR)	2 (2–3)	Median ASPAT level (IQR)	61 IU/l (47.5–75)
Median of the highest, degrees (IQR)	39 (38.7–40)	Complications	
Rash		No complications, n (%)	27 (32.14)
Presence, n (%)	84 (100.00)	Pneumonia, n (%)	39 (46.43)
Present on the day of admission, n (%)	15 (17.86)	Otitis, n (%)	19 (22.62)
Present the day before admission, n (%)	31 (36.90)	Hepatitis, n (%)	8 (9.52)
Present two days before admission, n (%)	15 (17.86)	Otitis and pneumonia, n (%)	7 (8.33)
Median duration (IQR)	5 (4–6)	Diarrhoea, n (%)	10 (11.90)
Median duration before admission (IQR)	1 (1–2)	Treatment	
Median day with highest intensity (IQR)	2 (2–3)	One antibiotic, n (%)	48 (57.14)
Typical mileage and appearance, n (%)	61 (72.62)	At least 2 antibiotics, n (%)	10 (11.90)
Other typical symptoms		Cefuroxime, n (%)	27 (32.14)
Cough, n (%)	78 (92.86)	Amoxicillin, n (%)	13 (15.48)
Coryza, n (%)	55 (65.48)	Ceftriaxone, n (%)	10 (11.90)
Conjunctivitis with photophobia, n (%)	33 (39.29)	Azithromycin, n (%)	2 (2.38)
Koplik spots, n (%)	56 (66.67)	Clarithromycin, n (%)	1 (1.19)
Hepatomegaly, n (%)	47 (55.95)	Ampicillin, n (%)	1 (1.19)
Splenomegaly, n (%)	28 (33.33)	Nystatin, n (%)	38 (45.24)
Vomiting, n (%)	10 (11.90)	Corticosteroids, n (%)	20 (23.81)
Lymphadenopathy, n (%)	35 (41.67)	B2 memetics, n (%)	7 (8.33)

IQR – interquartile range

shorter, compared to children younger than 12 months and those older than 15 years ($p < 0.02$) [18]. According to Ben-Chetrit *et al.* the average length of hospitalisation due to measles in patients under 20 years of age was 3 days [9]. In the same study, in children younger than

5 years, re-hospitalisation within 90 days was required in 9.4% of cases [9]. According to Lo Vecchio *et al.*, the average length of children's hospitalisation was 5 days [4]. The result of our study positioned between with a median of 4 days (IQR: 3–5). Most patients were admit-

TABLE 2. Characteristics of symptoms and complications occurring in hospitalised infants and older children due to measles January 2017 – December 2019 in the Department of Children's Infectious Diseases in Warsaw

Characteristic	Total (N = 84)	Infants (n = 26)	Older children (n = 58)	p-value
Fever, n (%)	84 (100.00)	26 (100.00)	58 (100.00)	–
Rash, n (%)	84 (100.00)	26 (100.00)	58 (100.00)	–
Cough, n (%)	78 (92.86)	24 (92.31)	54 (93.10)	0.895841
Conjunctivitis, n (%)	75 (89.29)	21 (80.77)	54 (93.10)	0.091092
Photophobia, n (%)	33 (39.29)	6 (23.08)	27 (46.55)	0.041693
Coryza, n (%)	55 (65.48)	14 (53.85)	41 (70.69)	0.133345
Koplik spots, n (%)	56 (66.67)	18 (69.23)	38 (65.52)	0.133345
Lymphadenopathy, n (%)	35 (41.67)	5 (19.23)	30 (51.72)	0.005229
Hepatomegaly, n (%)	47 (55.95)	10 (38.46)	37 (63.79)	0.030619
Splenomegaly, n (%)	28 (33.33)	4 (15.38)	24 (41.38)	0.019469
Vomiting, n (%)	10 (11.90)	5 (19.23)	5 (8.62)	0.165085
Otitis, n (%)	19 (22.62)	10 (38.46)	9 (15.52)	0.020141
Diarrhoea, n (%)	10 (11.90)	5 (19.23)	5 (8.62)	0.165085
Pneumonia, n (%)	39 (46.43)	10 (38.46)	29 (50.00)	0.326948
Hepatitis, n (%)	8 (9.52)	2 (7.69)	6 (10.34)	0.701819

ted to the hospital on the day of the rash onset (28.3%, $n = 88$) or the day after the rash appeared (27.8%, $n = 381$). A total of 15.7% of patients ($n = 213$) were admitted to the hospital during the prodromal phase of the disease (1–4 days before the rash onset), while 26.3% of patients ($n = 358$) were admitted to the hospital at least 2 days after the rash onset, due to measles complications [17]. In our study, the rash appeared most often the day before admission, this occurred in 31 patients (36.90%), in 15 (17.86%) patients 2 days before admission, and in 15 (17.86%) patients on the day of admission. The rash usually disappears after 5 days, but Battagay *et al.* found that in some cases it disappeared after the seventh day of the symptoms onset [19]. In our study we obtained similar results, in which the median length of the rash was 5 days (IQR: 4–6 days). At the latest, it began to disappear after 11 days. The median highest severity of the rash occurred on day 2 (IQR: 2–3 days).

Hepatomegaly is a nonspecific symptom that sometimes occurs in patients infected with measles virus. Sunnetcioglu *et al.* showed that of 50 adult patients, only 4% of patients had an enlarged liver [20]. In our study, the proportion of patients with hepatomegaly was much higher (47/84, 55.95%), which may suggest that hepatomegaly is more common among the paediatric population.

According to Sunnetcioglu *et al.* lymphadenopathy was present in only 12% of patients [20]. In a study by Han *et al.*, which included a large, age-diverse population (8224 participants), its incidence was 9.4% [21]. In our study, enlarged lymph nodes were reported in 35 children (41.67%), of which cervical lymph nodes were involved in 40% of cases, and mandibular angle nodes in 22.86%. In an observational study by Atti *et al.*, pneumonia was

a complication in 2.17% of children overall, and in 10% of hospitalised children [22]. In children under 10 years of age, this rate was 41%, with the highest rate in infants (47.9%) [23]. In our study, 46.43% of the observed children had pneumonia. Another common complication is otitis media. According to Atti *et al.*, this was the most common complication in the studied paediatric population (3.9%); however, among hospitalised children, it was only 1.2% [22]. In our study, otitis media was registered in 22.62% of children, of which 8.33% occurred concurrently with pneumonia. Another common complication is diarrhoea, which registers at 22.9–24% in children hospitalised for measles [4, 23]. According to Ben-Chetrit *et al.*, in hospitalised patients in the general population, this proportion is lower, equal to 11.2% [9]. In our study, diarrhoea was reported in 11.90% of cases. According to Han *et al.*, in the general population, hepatitis during measles occurs in 7.2% of affected patients [21]. In hospitalised children, in the study by Lo Vecchio *et al.* this proportion was 6% [4]. In this study, that rate was slightly higher at 9.52%.

Lo Vecchio *et al.* showed that 16.5% of children admitted to the hospital had thrombocytopenia, 40.6% had leukopenia, and 22.9% had neutropenia [4]. According to Atti *et al.*, 0.6% of hospitalised patients had thrombocytopenia [22]. In our study, 78.57% of participants had at least one abnormality in laboratory tests. Specifically, 16.67% of patients had leukopenia, 10.71% had neutropenia, and 1.19% had thrombocytopenia.

When the course of measles is complicated by other bacterial infections, antibiotic treatment is required. Ben-Chetrit *et al.* indicated that antibiotic therapy was implemented in 71/161 (44%) patients [9]. In contrast, referring to Lo Vecchio *et al.* who studied the effect of vi-

tamin A on the clinical course of measles and the occurrence of complications, antibiotic therapy was needed in 68/108 (62.96%) patients, and the effect of vitamin A was not statistically significant [24]. In our study, 48/84 (57.14%) patients were treated with one antibiotic, while 10 patients (11.90%) required at least 2 antibiotics.

Sindhu *et al.* examined differences in clinical presentation between infants and older children in 58 paediatric patients hospitalised for measles. No significant differences in typical measles symptoms were noted, except for the more frequent appearance of a rash within 3 days of the onset of fever and the more frequent presence of complications in infants [25]. In our study, infants had significantly less frequent photophobia ($p = 0.041693$), lymphadenopathy ($p = 0.005229$), hepatomegaly ($p = 0.030619$), and splenomegaly ($p = 0.019469$). Instead, they were significantly more likely to have acute otitis media ($p = 0.020141$).

LIMITATIONS

The study we conducted has several limitations, including being a single-centre retrospective study. This resulted in the inability to complete some of the information on the patients' disease course. The department where the study was conducted is the largest paediatric infectious disease centre in Poland with experienced medical staff, which increases the likelihood of an appropriate diagnosis and treatment. Another advantage of our study is the relatively large population of patients.

CONCLUSIONS

Measles is a serious disease that mostly affects unvaccinated children, which is why early vaccination of children and post-exposure prophylaxis are so crucial. The most common symptoms include fever and rash, which occurred in all our patients. A high proportion of patients developed complications, the most common of them were otitis media and pneumonia. Because many as more than a half of hospitalised children required treatment with at least one antibiotic. The differences in symptoms and complications of measles differ significantly between infants and older children. Less typical symptoms such as splenomegaly and hepatomegaly are more common in the older children, while more typical symptoms such as photophobia and lymphadenopathy were less common in infants. These features contribute to the significant difficulties in the clinical diagnosis of measles.

DISCLOSURES

1. The study was approved by the Bioethics Committee: AKBE/114/22.

2. The data sets used and/or analysed during the current study can be made available by the corresponding author on reasonable request.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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