Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 45 (1988)
Heft: 4

Artikel: Human monkeypox : confusion with chickenpox
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DOI: https://doi.org/10.5169/seals-314088

Acta Tropica 45, 297–307 (1988)

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Human monkeypox: confusion with chickenpox

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Summary

Human monkeypox is a zoonosis occurring sporadically in the tropical rain forest of western and central Africa. The exact incidence and geographical distribution are unknown, since many cases are not recognized. Special surveillance was established in three regions in Zaire in 1981 that led to a substantial increase in reported cases. The question arose as to the possibility that clinical diagnostic errors cause some cases of monkeypox to be misdiagnosed as other eruptive diseases. This paper presents the results of a study assessing the extent of and reasons for these clinical diagnostic errors in areas where health staff as well as the general public are aware of human monkeypox. In Zaire in the period 1981–1986, 977 persons with skin eruption not clinically diagnosed as human monkeypox were laboratory tested. 3.3% of human monkeypox cases were found among 730 patients diagnosed as cases of chickenpox, 7.3% among cases diagnosed as "atypical chickenpox" and 6.1% among cases with skin rash for which clinical diagnosis could not be established. The diagnostic difficulties were mainly based on clinical features characteristic of chickenpox: regional pleomorphism (in 46% of misdiagnosed cases), indefinite body-distribution of skin eruptions (49%), and centripetal distribution of skin lesions (17%). Lymph-node enlargement was observed in 76% of misdiagnosed patients. In the absence of smallpox, the main clinical diagnostic problem is the differentiation of human monkeypox from chickenpox. The presence of lymphadenopathy, pre-eruptive fever and slower maturation of skin lesions are the most important clinical signs supporting correct diagnosis of monkeypox.

Key words: human monkeypox; clinical and differential diagnosis; zoonosis.

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Introduction

Human monkeypox is a rare zoonosis occurring in the tropical rain forest areas of western and central Africa. It is a disease with several similarities to smallpox: the pathogenic agents are both Orthopoxviruses, clinical manifestations and course of illness are almost similar. However, epidemiological features of human monkeypox are different. The most important differences are the sporadic nature of human monkeypox occurrence and its low secondary inter-human transmission rate (Jezek et al., 1986). The exact incidence of human monkeypox and its actual geographical distribution in Africa are not yet well known, since many cases are not recognized and thus not reported. Occurrence of the disease in relatively remote areas with few medical personnel, usually unfamiliar with the disease, and the possible confusion with other skin rash diseases, are the main reasons for this situation.

In 1979, the Global Commission for the Certification of Smallpox Eradication believed human monkeypox to be the most important orthopoxvirus infection in the post-smallpox era, and one that required special epidemiological surveillance (WHO, 1980) so that more could be discovered about the natural history of the disease, its epidemiology and clinical features. Special surveillance activities were established in three regions of Zaire in 1981, with participation of local health establishments and mobile surveillance teams. This led to a substantial increase of reported cases of human monkeypox (WHO, 1984), based primarily on better recognition of the illness by trained medical staff and by recognition of additional cases which were originally misdiagnosed as other eruptive diseases, but proved to be cases of human monkeypox by subsequent laboratory diagnostic tests.

This article reports on results of a study assessing the extent and reason for clinical diagnostic errors concerning human monkeypox cases in areas where health staff and the local population know about human monkeypox.

Materials and Methods

The study was carried out in three regions of Zaire, namely Equateur (sub-regions: Mongala and South Ubangi), East Kasai (Sankuru) and Bandundu (Kwango and Kwilu), where special monkeypox surveillance systems were established in 1981.

Health-institution-based surveillance became the backbone of this system. This depended upon collaboration of hospital and dispensary staff of approximately 150 peripheral health establishments, most of them covering areas with dense tropical rain forest. Their primary responsibility was detection, clinical examination and reporting of suspected monkeypox patients as well as other persons with vesiculo-pustular or crusting skin rash, and collection/despatch of specimens for laboratory testing. About 20% of the initial diagnoses were made by the physicians, who were present at the time of the patients' admission; the rest of the initial diagnoses were made by medical assistants or nurses at the time of the patients' admission and verified by a collaborating physician later. The activities of health establishment were supported by mobile teams and special surveillance agents who carried out investigations of persons with skin eruptions, actively detected in villages or notified by local headmen or the public. Mobile teams also collected and despatched skin/serum specimens

Table 1. Relationship between clinical diagnosis and laboratory confirmed diagnosis for human monkeypox and other skin eruptive diseases

Clinical diagnosis	Laboratory diagnosis		
	Monkeypox	Other eruptive disease	Total
Monkeypox	286	87	373
Other eruptive diseases	41	936	977
Total	327	1023	1350

for subsequent laboratory testing. A monetary reward of 500 zaires (approximately US$ 80) was offered to any person, including health staff, who reported a case of human monkeypox which was subsequently confirmed by laboratory tests.

Laboratory examinations for the presence or absence of monkeypox virus or monkeypox virus specific antibodies in tested specimens were made by the WHO Collaborating Centres at the Centres for Disease Control, Atlanta, USA, and at the Research Institute for Viral Preparations, Moscow, USSR. Vesicular and pustular fluids and scabs were examined by electron microscopy and cultured on chicken embryo chorioallantoic membrane and in tissue culture. Sera were examined by haemagglutination-inhibition (HI) test, fluorescent antibody (FA) test, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and radioimmunoassay adsorption (RIAA) test in Atlanta or by ELISA and ELISA-adsorption test in Moscow (Marennikova et al., 1984; Maltseva et al., 1984; Nakano, 1985; Jezek et al., 1987a).

Statistical evaluation: Statistical significance was assessed by using χ^2 test with Yates correction for continuity.

Results

During the six-year period 1981–1986, a total of 373 initially clinically diagnosed cases of human monkeypox were reported from the three regions of Zaire covered by special surveillance with a population of about 8 million (Table 1). Laboratory examination confirmed the diagnosis of human monkeypox for 286 patients (77% of all initially suspected cases).

In addition to the clinically diagnosed monkeypox patients, a further 977 persons living in the study area who developed skin eruptions but were not suspected to be monkeypox patients, were clinically examined and their skin lesions specimens and/or serum collected for laboratory testing. Out of them 41 persons (i.e. 4.2%) were identified by laboratory tests as cases of human monkeypox, augmenting their total number to 327 patients (Table 1).

Table 2 presents the age and sex distribution and vaccination status of all 977 patients clinically diagnosed as cases of eruptive diseases other than monkeypox.

Most of them (68%) were children under 15 years of age. 54% were below 10 years and 33% below 5 years of age. They were equally distributed by sex.

Table 2. Observed patients* by age, sex and vaccination status

Age group	Males	Females	Total examined		Vaccination scar		
			No.	%	Present	Absent	
						No.	%
0	38	52	90	9.2	0	90	100.0
1–4	114	117	231	23.6	34	197	85.3
5–9	106	105	211	21.6	127	84	39.8
10–14	61	71	132	13.5	100	32	24.2
15–19	37	41	78	8.0	71	7	9.0
20–29	63	57	120	12.3	112	8	6.7
30–39	27	16	43	4.4	39	4	9.3
40 +	43	29	72	7.4	61	11	15.3
Total	489	488	977	100	544	433	44.3

* clinically diagnosed as cases of skin eruptive diseases other than monkeypox

44% of them had no visible vaccination scars as routine vaccination against smallpox was terminated in 1980. 57% of the patients visited peripheral health establishments where clinical diagnosis was initially established and the remaining 43% were examined and diagnosed at home by visiting health staff, mobile teams or surveillance agents.

Table 3 shows the distribution of the same patients according to three classes of initial clinical diagnosis as recorded on individual history forms, as well as the distribution of those who turned out to be actually monkeypox patients, identified by subsequent laboratory tests.

Out of the total of 730 patients diagnosed according to current clinical signs and symptoms as cases of chickenpox, whose specimens were further laboratory tested, the presense of monkeypox virus and/or monkeypox virus-specific antibodies were discovered in samples of 24 patients, i.e. an overall proportion of misdiagnosis of 3.3%. The rate varied with age, the highest one (6.6%) being found in the 5 to 9-year age group. Among the 165 cases diagnosed as "atypical chickenpox" 12 cases of misdiagnosed monkeypox were identified by laboratory tests, that is an overall proportion of 7.3% – the highest from all three investigated groups. The rate varied also with age, the highest one (13.9%) being found among younger children in the 1 to 4-year age group. Five misdiagnosed monkeypox patients (6.1%) were found among the 82 patients with skin eruptions for which the clinical diagnosis could not be determined. No sex difference in the rates were found in any of the three diagnostic groups.

The main clinical features observed in the 41 clinically misdiagnosed patients are described below. They are also compared with the corresponding signs and symptoms observed in the 286 initially correctly diagnosed monkeypox patients.

Only in 10% of the monkeypox patients initially misdiagnosed did the illness begin with skin rash. The majority of these patients (83%) had fever which lasted for 1 to 3 days before rash occurred. The remaining 7% of patients had fever more than 3 days. In most patients febrile illness was accompanied by headache, shivering and malaise. In many patients enlargement of lymph nodes was observed before onset of rash. Similar frequencies were observed in the group of initally correctly diagnosed patients.

Table 4 summarizes the main characteristics of exanthema in the 41 misdiagnosed and the 286 initially correctly diagnosed monkeypox patients. Regional monomorphism (i.e. same skin form throughout all stages of development) of skin lesions ($\chi^2 = 12.12$; $p < 0.001$) and centrifugal body distribution of the rash ($\chi^2 = 49.59$; $p < 0.001$) were significantly better expressed among those initially correctly diagnosed than among misdiagnosed patients. Pleomorphism caused by "cropping" occurred in 46% of clinically misdiagnosed and 20% of correctly diagnosed patients. Indefinite or centripetal body-distribution of skin rash was observed in 66% of misdiagnosed patients in contrast to 16% of those rightly diagnosed. For both diagnostic groups the skin rash was discrete (i.e.

Table 3. Patients by age, initial clinical diagnosis and laboratory confirmed diagnosis of monkeypox

Age group	Chickenpox			Atypical chickenpox			Skin eruptions		
	Total observed No.	From them monkeypox		Total observed No.	From them monkeypox		Total observed No.	From them monkeypox	
		No.	%		No.	%		No.	%
0	61	1	1.6	19	1	5.3	10	0	*
1–4	169	8	4.7	43	6	13.9	19	2	*
5–9	166	11	6.6	29	2	6.9	15	2	*
10–14	110	2	1.8	17	1	5.9	5	1	*
15–29	141	1	0.7	40	1	2.5	18	0	*
30 +	83	1	1.2	17	1	5.9	15	0	*
Total	730	24	3.3	165	12	7.3	82	5	6.1

* small numbers

Table 4. Main characteristics of exanthema in 41 clinically misdiagnosed and in 286 initially rightly diagnosed monkeypox patients

Characteristics of exanthema	Monkeypox patients clinically			
	misdiagnosed[a]		rightly diagnosed[b]	
	No.	%	No.	%
Regional occurrence				
monomorphism	22	53.6	228	79.7
pleomorphism	19	46.4	58	20.3
Extent				
discrete	27	65.9	173	60.5
semi-confluent	14	34.1	83	29.0
confluent	–	–	30	10.5
Body distribution				
centrifugal	14	34.1	241	84.3
centripetal	7	17.1	12	4.2
indefinite	20	48.8	33	11.5
Presence of pocks				
facial	35	85.3	234	81.8
palmar	22	53.6	187	65.4
plantar	10	24.4	196	68.5

[a] patients initially clinically misdiagnosed as cases of chickenpox, "atypical" chickenpox or "skin eruption", with laboratory confirmed diagnosis of monkeypox

[b] patients initially clinically diagnosed as cases of human monkeypox and subsequently confirmed by laboratory tests

skin lesions separated by normal skin) in about two thirds, and semi-confluent rash (i.e. confluent on the face) in about one third of the patients. Pocks on palms and soles were more frequent in correctly diagnosed patients than in those who had been misdiagnosed.

Sore throat was a common feature of the early stage of illness in both groups of observed patients. Enathema in the oral cavity (vesicles or shallow ulcers) was present in 56%, lesions on genitalia causing irritation in 29% and lesions on the edges of the eyelids and conjunctiva in 24% of the misdiagnosed cases. These rates did not differ significantly from those observed in the group of correctly diagnosed patients.

Temporary enlargement of lymph nodes was observed in 76% of misdiagnosed and 83% of correctly diagnosed patients (Table 5). In the majority of cases in both groups lymphadenopathy occurred early, often at the time of onset of fever or on the second or third day of illness. Early enlargement of the lymph nodes was more common in the neck area (submaxillar and cervical nodes) but

Table 5. Frequency and sites of lymph-node enlargement in 41 clinically misdiagnosed and 286 initially rightly diagnosed monkeypox patients

Lymph-node enlargement	Monkeypox patients clinically			
	misdiagnosed[a]		rightly diagnosed[b]	
	No.	%	No.	%
Present	31	75.6	237	82.9
Absent	10	24.4	49	17.1
One lymph-node bearing area*	13	31.7	56	19.6
– submaxillar	2		14	
– cervical	8		18	
– axillar	0		7	
– inguinal	3		17	
Two lymph-nodes bearing area*	4	9.8	25	8.7
Generalized lymphadenopathy	14	34.1	156	54.5

*unilateral or bilateral

[a] patients initially clinically misdiagnosed as cases of chickenpox, "atypical" chickenpox or "skin eruptions", with laboratory confirmed diagnosis of monkeypox

[b] patients initially clinically diagnosed as cases of human monkeypox and subsequently confirmed by laboratory tests

lymph nodes in other node-nearing areas were usually enlarged later in the course of illness. Generalized lymphadenopathy was observed in 34% of misdiagnosed monkeypox cases and 55% of the correctly diagnosed patients. This difference was statistically significant ($\chi^2 = 5.191$; $p < 0.005$).

Four initially misdiagnosed monkeypox cases ended fatally, the crude case/fatality rate being 9.8%. The number of deaths was 28 among the 286 correctly diagnosed monkeypox patients, reflecting the same case fatality rate (9.8%).

Discussion

Among the 373 patients clinically diagnosed as monkeypox cases, 87 were not confirmed by laboratory tests (Table 1). For this group of false positives the source of misdiagnosis was more epidemiological than clinical: the majority of them were unvaccinated children, living in villages where monkeypox cases occurred recently, having been in contact with arboreal rodents or monkeys during the three weeks preceding the onset of illness and with the initial diagnosis having been done within the first three days of skin rash.

This kind of overdiagnosis seems to be common in areas where specific

disease oriented surveillance campaigns are performed. Incidentally, the satisfactory performance of the surveillance teams and health staff from peripheral health establishments is illustrated by quite reasonable sensitivity (87.5%) and particularly high specificity (91.5%) of the clinical diagnosis.

Outside areas with the special surveillance the situation is quite different. Only a small fraction of human monkeypox cases that actually occur in western and central Africa are seen or recognized by health staff. The main reasons for this include: (i) occurrence of disease in relatively remote areas with few medical services; (ii) lack knowledge and unfamiliarity of medical personnel with the disease and a low "index of suspicion", (iii) confusion with other endemic diseases, i.e., chickenpox, (iv) lack of access to laboratory diagnostic tests, and (v) inefficient disease reporting and difficult communications.

Clinicians working in tropical rain forest areas in Africa should consider human monkeypox in (i) any patient suspected to be a case of smallpox, (ii) any unvaccinated person, particularly a child who comes from a forest area to hospital or dispensary with febrile illness, lymphadenopathy and vesiculopustular or crusting skin rash for which diagnosis cannot be determined, (iii) any patient dying in vesiculo-pustular stage of the illness or dying with diagnosis of "chickenpox", and (iv) in any patient having "*atypical*" rash due to chickenpox or other eruptive illnesses.

After the eradication of smallpox, the main clinical diagnostic problem is differentiating human monkeypox from chickenpox. Clinical features of chickenpox and finer points of differentiating chickenpox from smallpox are described (Christie, 1980; Juel-Jensen and Maccallum, 1972) and generally known. The clinical picture of human monkeypox is similar to the ordinary and modified forms of smallpox (Jezek et al., 1987b; Fenner et al., 1988); however, several clinical signs and symptoms vary more widely, contributing to incorrect diagnosis. In the present study, pleomorphisms of skin lesions occurring in many of the misdiagnosed patients (Table 4), among whom the indefinitive distribution or concentration of the skin rash on the trunk rather than the limbs and absence of pocks on palms and soles, was more suggestive of chickenpox than human monkeypox.

In particular, "croppping" of the rash, a well-known sign in chickenpox, was observed in 46% of the misdiagnosed cases but also in 20% of the correctly diagnosed patients, so its diagnostic importance in differentiation from human monkeypox must not be exaggerated.

The most important clinical sign differentiating human monkeypox from chickenpox (and smallpox) is the pronounced lymph-node enlargement, occurring in the early stage of illness, which was present in 76% of the misdiagnosed and 83% of the correctly diagnosed monkeypox patients (Table 5). In most of the misdiagnosed cases, as well as in the correctly diagnosed monkeypox cases, the prodromal illness starting with fever was indistinguishable from smallpox but differed from chickenpox. Another important sign in the dif-

ferential diagnosis is the maturation of the skin lesions. The skin rash in both the misdiagnosed as well as the correctly diagnosed monkeypox patients did not mature so quickly as in chickenpox; no lesions were observed drying up and beginning to crust within 48 hours of their appearance as in chickenpox. According to present experience, presence of lymphadenopathy, pre-eruptive fever and slower maturation of skin lesions belong to important differential signs and symptoms, supporting the correct diagnosis of monkeypox.

Many infectious diseases are usually recognized during epidemics or in outbreaks when the disease could be observed in many individuals and is therefore relatively easily diagnosed clinically. This is the case with chickenpox, contrary to human monkeypox where the majority of cases occur sporadically and as solitary ones. In human monkeypox, as in other communicable diseases, there are three elements for correct diagnosis, clinical epidemiological and laboratory. As experience shows, no one diagnostic approach is ever sufficient in itself. There are always patients in whom accurate diagnosis could not be made on clinical grounds alone. Considerable help may be obtained by the examination of specimens in specialized laboratories, either by recovery of the virus from lesion material or retrospectively by appropriate serological tests. Unfortunately at present this is not easily accessible for many peripheral health establishments located in affected enzootic areas.

It is widely recognized that only a fraction of communicable disease cases are reported. The situation in human monkeypox is similar, if not worse, since cases are not recognized, even not suspected. Good knowledge of the disease and requirement of its reporting need greater emphasis at every level of the medical and public health services working in forest areas in western and central Africa.

Acknowledgments

We thank the staff of participating health establishments and surveillance teams for recording and collection of samples, and Dr. S. S. Marennikova, Research Institute for Viral Preparations, Moscow, USSR, and Dr J. H. Nakano, Centres for Disease Control, Atlanta, USA, for laboratory examinations.

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