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Clinico-epidemiological features of monkeypox patients with an animal or human source of infection

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Clinical and laboratory examinations were carried out on a total of 338 monkeypox patients in Zaire from 1981 to 1986. An animal source of infection was suspected in 245 (72%) and interhuman transmission for the remaining 93 patients. Among those whose infection was presumably acquired from an animal source, the most affected groups were children aged 3–4 years (27%) and 5–6 years (20%), while only 4% of cases were over 15 years old; there was a considerable preponderance of males (58%) over females (42%), especially in the age group 5–14 years. Among those presumably infected by person-to-person transmission, the age distribution was more uniform, adult patients tending to be relatively more common, and there were more females (57%) than males (43%).

Based on comparisons of the frequency and intensity of clinical signs and symptoms among patients infected from an animal source and those who were infected by another patient, there was no evidence that the disease becomes more severe and the transmitted virus more virulent or more easily transmissible from person to person after one or more passages through human hosts.

Between 1970, when the first case of human monkeypox was discovered (*1, 2*) in Equateur province of the Democratic Republic of the Congo (named Zaire in 1971), and the end of 1986 a total of 404 monkeypox patients have been reported in seven countries of West and Central Africa. These cases occurred either singly or in small clusters in small villages located in tropical rain forests where the inhabitants usually have numerous contacts with a variety of wild animals. Monkeypox is considered to be a classical zoonosis, the majority of human infections being attributed to contact with affected animals. Nevertheless, there is increasing evidence of human-to-human transmission of the monkeypox virus (*3–6*).

This finding raised an important question: does the monkeypox virus change when it passes through a human host, so that it can more easily infect other humans? An answer to this question should contribute to a better understanding of the transmission potential of monkeypox virus and its possible persistence in human communities through continued person-to-person transmission. A strain of virus is said to become more or less virulent if it regularly produces, respectively, more severe or less severe disease in a particular host species. Active surveillance of human monkeypox, which has been carried out in Zaire since 1981 (*7*), now provides information for comparing the extent and intensity of the principal signs and symptoms, the course of the illness, the frequency of complications, and the outcome of human monkeypox cases due to infection from animal and human sources.

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MATERIALS AND METHODS

Since 1981, active surveillance has been greatly intensified in five areas of dense tropical forest in Zaire, with the participation of some 150 health establishments and four mobile surveillance teams (*7*). Each team, composed of an experienced physician and one or two nurses and health inspectors, paid several visits to localities where monkeypox patients had been reported. Patients with fever that was followed by skin eruptions were examined and clinico-epidemiological diagnoses were subsequently verified by laboratory testing of specimens of skin lesions, or serum, or both. Follow-up visits to the affected locality were made every 7–10 days for determining the patients' clinical status and collecting further specimens, and finding out whether any new cases had occurred among the close contacts.

In all the field investigations, careful attention was given to the possible source of infection (animal or human). Considerable weight was placed on confirming clinico-epidemiological diagnoses by laboratory tests, which were carried out by the WHO Collaborating Centres at the Centers for Disease Control in Atlanta, USA, and at the Research Institute for Viral Preparations in Moscow, USSR. Vesicular and pustular fluids and scabs were examined by electron microscopy and cultured on the chorioallantoic membrane and in tissue culture. Sera were examined by the haemagglutination inhibition (HAI) test, fluorescent antibody test, ELISA, radioimmunoassay (RIA), and the RIA adsorption test. Sera were also tested for antibody to varicella-zoster virus by a fluorescent antibody test and ELISA.

Statistical significance was assessed by the χ^2 test with Yates' correction for continuity.

Definitions

In the analysis of the transmission pattern, the *primary case,* who presumably was infected from an animal source, is the first one occurring in a focus. A subsequent case among the contacts, whose onset of illness occurred within 7 days of the onset of rash in the primary case and is attributable to the same animal source of infection, is regarded as a *co-primary case.* A patient in whom the rash appeared between 7 and 21 days after exposure to another human case is considered to be a *secondary case,* which may have arisen by person-to-person transmission.

RESULTS

Persons affected

A total of 338 human monkeypox patients, 182 males and 156 females, were reported in Zaire during the period 1981–86. Their ages ranged from three months to over 69 years (mean age: 6.9 years), but because the majority were in the younger age groups the median age was only 4.4 years.

An animal source of infection was suspected in 245 cases (72.5%) and a human source in the remaining 93 cases (27.5%). Patients who were presumably infected from an animal source (Table 1) were mostly children aged 3–4 years (27%), followed by those aged 5–6 years (20%); the proportions then decreased with age, being lowest in adults (4%). There was a considerable preponderance of males over females, especially in the age group 5–14 years.

A more uniform age distribution pattern was found among those presumed to have been infected from

Table 1. Distribution of 338 monkeypox patients by presumed source of infection, age group and sex

	Infection from animal source			Infection from human source		
Age group (years)	Males	Females	Total	Males	Females	Total
<1	8	8	16 (6.5)[a]	3	8	11 (11.8)
1–2	21	26	47 (19.2)	9	8	17 (18.3)
3–4	33	34	67 (27.3)	10	7	17 (18.3)
5–6	32	17	49 (20.0)	6	9	15 (16.1)
7–9	30	6	36 (14.7)	6	10	16 (17.2)
10–14	14	7	21 (8.6)	2	1	3 (3.2)
⩾15	4	5	9 (3.7)	4	10	14 (15.1)
Total	142 (58.0)	103 (42.0)	245	40 (43.0)	53 (57.0)	93

[a] Figures in parentheses are percentages.

a human source, in which group infants and adult patients tended to be relatively more common. There was also a significant ($\chi^2=5.475$; $P<0.05$) preponderance of females (57%) over males (43%), compared with the group of primary cases (42% females and 58% males).

Forty-three out of the 338 patients (13%) had a visible vaccination scar(s); this includes five persons with a doubtful vaccination scar but with a history of vaccination. The proportion of vaccinated persons was significantly less among patients suspected of having been infected from an animal source (23/245=9%) than among those presumably infected from a known human source (20/93=22%; $\chi^2=7.857$; $P<0.01$). Since residual immunity caused by past vaccination substantially reduced the frequency and intensity of clinical signs and symptoms (*8*), only individuals without a visible vaccination scar were considered in subsequent analyses.

Clinical features

The main clinical features of 222 unvaccinated patients suspected to have been infected from an animal source and 73 cases infected from a human source were compared. No differences were found in the frequency and extent of clinical signs and symptoms, by age and sex, between the two groups.

The main characteristics of the exanthem in the two groups are shown in Table 2. There was no significant difference between the morphology and distribution of skin lesions, but patients with a confluent rash on the face and forearms formed a higher proportion among the primary cases ($\chi^2=4.834$; $P<0.05$). The proportion of patients with 500 or more skin lesions was also significantly higher ($\chi^2=4.567$; $P<0.05$) among primary cases than among secondary ones.

Lesions on various mucous membranes were observed in 79% of primary and 68% of secondary cases (Table 3). Enanthem in the oral cavity was observed significantly more frequently in the primary cases (75%) than in secondary ones (56%) ($\chi^2=8.225$; $P<0.01$). Acute tonsillitis was found in 54% of primary cases and 40% of secondary cases, the difference being just below the 5% significance level. Coughing with or without sputum production was a relatively common symptom in both groups. Enlargement of lymph nodes occurred in the great majority of cases. Generalized lymphadenopathy was more frequently observed in primary cases (58%) than in secondary ones (48%).

Duration and outcome. The illness lasted between two and four weeks. There was no significant difference in the duration according to the origin

Table 2. Distribution of the main characteristics of the exanthem in unvaccinated monkeypox patients, by presumed source of infection

Characteristics	Infection from animal source	Infection from human source
Occurrence:		
Monomorphic[a]	176 (79.3)[b]	57 (78.1)
Pleomorphic[a]	46 (20.7)	16 (21.9)
Total observed	222	73
Lesions:		
Discrete	124 (55.9)	48 (65.8)
Semiconfluent	70 (31.5)	23 (31.5)
Confluent	28 (12.6)	2 (2.7)
Haemorrhagic	0 (0)	0 (0)
Total observed	222	73
Body distribution:		
Centrifugal	192 (86.5)	54 (74.0)
Centripetal	8 (3.6)	5 (6.8)
Indefinite	22 (9.9)	14 (19.2)
Total observed	222	73
Presence of pocks:		
Facial	196 (88.3)	60 (82.2)
Palmar	157 (70.7)	49 (67.1)
Plantar	156 (70.3)	40 (54.8)

[a] Monomorphic = all lesions at the same stage; pleomorphic = more than one crop of lesions.

[b] Figures in parentheses are percentages.

Table 3. Frequency of lesions on mucous membranes and of tonsillitis in unvaccinated monkeypox patients, by presumed source of infection

	Infection from animal source	Infection from human source
Total observed	222	73
Lesions on mucous membranes:[a]	175 (78.8)[b]	50 (68.5)
Oral	166 (74.8)	41 (56.2)
Conjunctival	45 (20.3)	12 (16.4)
Genital	74 (33.3)	14 (19.2)
Absent	47 (21.2)	23 (31.5)
Tonsillitis:		
Present	119 (53.6)	29 (39.7)
Absent	103 (46.4)	44 (60.3)

[a] For several patients more than one site was affected.

[b] Figures in parentheses are percentages.

of infection: 68% of primary cases and 74% of secondary cases recovered by the end of the third week of the illness.

Complications occurred in 41% of primary and 34% of secondary cases (Table 4). There were no significant differences between the groups in the frequency of complications as a whole or in the incidence of any particular complication. Serious sequelae, including unilateral or bilateral blindness, weak vision and deforming scars, were observed in 10% of primary and 5% of secondary cases. Based on the number of skin lesions and the severity of systemic symptoms and physical discomfort, the illness could be classified as mild, moderate or severe (Table 4); no significant differences were found between the two groups of cases.

Thirty-three deaths occurred among the 338 patients (crude case-fatality rate, about 10%). All the deaths occured among unvaccinated children between three months and eight years of age, the age-specific case-fatality rate for the 0–4-year age group (14.5%) being almost twice that for children in the 5–9-year age group (7.5%).

The crude fatality rate among patients infected from an animal source (11.7%) did not differ significantly from the rate found among patients exposed to a known human source (9.6%).

Table 4. Incidence of complications and severity of illness in unvaccinated monkeypox patients, by presumed source of infection

	Infection from animal source	Infection from human source
Complications absent	130 (58.6)[a]	48 (65.8)
Complications present:	92 (41.4)	25 (34.2)
Secondary bacterial infection of skin	38 (17.1)	10 (13.7)
Bronchopneumonia, pulmonary distress	26 (11.7)	8 (11.0)
Vomiting, diarrhoea, dehydration	18 (8.1)	4 (5.5)
Keratitis, corneal ulceration	8 (3.6)	3 (4.1)
Septicaemia	1 (0.5)	0 (0)
Encephalitis	1 (0.5)	0 (0)
Clinical severity:[b]		
Mild	17 (7.7)	5 (6.8]
Moderate	38 (17.1)	17 (23.3)
Severe	167 (75.2)	51 (69.9)
Total	222 (100)	73 (100)

[a] Figures in parentheses are percentages.

[b] *Mild* = 25 skin lesions, no incapacity. *Moderate* = 25–99 skin lesions; incapable of most physical activity and required nursing care. *Severe* = ⩾100 skin lesions; totally incapacitated and required intensive nursing care.

DISCUSSION

Between 1981 and 1986 a systematic effort was made to improve the detection, reporting and investigation of cases of human monkeypox in Zaire. This led to recognition of the fact that, although the majority of human infections result from close contact with infected animals, transmission of the monkeypox virus from person to person also occurs (*1, 5, 6*).

The disease was found to affect all age groups, but children under 10 years of age were at highest risk, accounting for 88% of primary and 82% of secondary cases. The preponderance of males (58%) over females (42%) among primary cases does not reflect the sex distribution in the general population (males 49%, females 51%) and must be attributed to a higher risk of infection for males. Young unvaccinated boys seem to be at special risk, perhaps because they trap small arboreal and terrestrial rodents and play more frequently with the carcasses of killed monkeys and other animals brought home by hunters. In contrast, females and adult patients were more common among secondary cases, probably because of more frequent infection of mothers by their sick children or of older sisters nursing their younger siblings.

The discovery of interhuman transmission of monkeypox virus raises an important question: does the virus change in virulence or pathogenicity as a result of passage through one or more human hosts? The observations reported here show that the virus retains its pathogenicity, since it produces typical signs and symptoms in secondary cases. Comparison of the frequency and intensity of clinical signs and symptoms between primary cases and secondary cases in unvaccinated patients showed that the infection tended to be slightly more severe among primary cases. Significantly higher proportions of confluent exanthem, more numerous skin lesions, and more frequent enanthem in the oral cavity were found in patients infected from an animal source. However, there were no significant differences between the two groups in the duration of illness, frequency of complications and sequelae, or severity of illness, as characterized by the extent of the body lesions, intensity of systemic symptoms, physical incapacity and need for special care, or the crude case-fatality rates.

There is therefore no evidence that the disease

becomes more severe and the transmitted virus more virulent or more easily transmissible to humans after one or more passages through human hosts. This is in agreement with field observations that the majority of introductions of monkeypox virus into human communities failed to give rise to even a single infection among contacts (*6*) and that human-to-human transmission of monkeypox virus occurs occasionally from primary human cases but very rarely from secondary cases (*4*). The longest reported chain of interhuman transmission of monkeypox virus consisted only of four serial cases (*5*).

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RÉSUMÉ

ASPECTS CLINIQUES ET ÉPIDÉMIOLOGIQUES DE L'ORTHOPOXVIROSE SIMIENNE CHEZ DES SUJETS INFECTÉS PAR CONTACT ANIMAL OU INTERHUMAIN

L'orthopoxvirose simienne est considérée comme une zoonose classique, la plupart des infections survenant chez l'homme pouvant être attribuées à un contact avec un animal malade. Néanmoins, il semble de plus en plus net qu'il existe une transmission de l'orthopoxvirus simien de personne à personne, ce qui amène à se poser une question d'importance: le virus de l'orthopoxvirose simienne se modifie-t-il lors du passage chez un hôte humain, acquérant ainsi une plus grande facilité à infecter d'autres sujets?

Une surveillance spéciale de l'orthopoxvirose simienne de l'homme, réalisée au Zaïre en 1981–1986, a permis de recueillir des informations comparatives sur les données épidémiologiques et cliniques, avec notamment une comparaison des signes et symptômes, de l'évolution de la maladie et de l'issue des cas dus à une infection contractée après contact avec un animal ou avec une personne infectée.

Sur 338 cas, une source animale d'infection a été suspectée chez 245 sujets (72%) et une transmission de personne à personne dans tous les autres cas. Chez les malades ayant selon toute vraisemblance contracté l'infection à partir d'une source animale, les groupes les plus atteints étaient les enfants de 3–4 ans (27%) et de 5–6 ans (20%), 4% seulement des cas touchant des sujets de plus de 15 ans. On observait une prépondérance remarquable des sujets de sexe masculin (58%) en particulier chez les 5–14 ans. Les jeunes garçons non vaccinés semblaient constituer un groupe à risque particulier car ils ont l'habitude de prendre au piège des petits rongeurs arboricoles et terrestres et jouent plus souvent que les filles avec les carcasses de singes et d'autres animaux rapportés par les chasseurs. Chez les sujets infectés à partir d'une source humaine, on observe une répartition plus uniforme selon l'âge, une prépondérance de cas féminins (57%) et une fréquence relativement plus élevée de cas adultes.

Afin d'évaluer les modifications éventuelles de la virulence du virus lors de son passage chez un ou plusieurs hôtes humains, on a comparé la fréquence et l'intensité des signes cliniques observés chez les sujets infectés à partir d'un animal à ceux observés chez les sujets infectés par contact avec un malade. Chez les sujets infectés par un animal, on a observé avec une fréquence sensiblement plus élevée des exanthèmes de type confluent, des lésions cutanées et des énanthèmes de la cavité buccale. En revanche, il n'existait pas de différences significatives de la durée de la maladie et de la fréquence des complications et des séquelles, ni de la gravité de la maladie, caractérisée par les taux bruts de létalité, le degré d'invalidité et la nécessité de soins spécialisés.

Rien ne montre donc que la maladie soit plus grave et que le virus transmis soit plus virulent ou plus facilement transmissible d'une personne à l'autre après un ou plusieurs passages chez un hôte humain.

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