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ORGANISATION MONDIALE DE LA SANTÉ

SE/72.1

ENGLISH ONLY

CLINICAL SMALLPOX
CLASSIFICATION AND FREQUENCY OF TYPE OF VARIOLA MAJOR

by

A. R. Rao
Health Officer, Corporation of Madras

Introduction

The clinical picture of smallpox is not always classical but varies from patient to patient depending upon the immunity status of the individual, the variety and perhaps other factors. For purposes of diagnosis as well as prognosis, the clinician, therefore, should be acquainted with the different clinical varieties. Recent studies in Madras by the author have also shown that the clinical variety of smallpox may also be correlated with the rate of transmission of infection to exposed contacts.

Existing classification

The old classification of smallpox cases (Curschmann, 1875)[1] into the haemorrhagic form, consisting of two types "purpura variolosa" and "variola pustulosa haemorrhagica" and the non-haemorrhagic form consisting of the "confluent", the "semi-confluent", the "discrete", and the "modified" types is still followed by some. This classification is based principally on the density of rash. Extensive clinical experience has shown that this classification does not provide much help either with respect to diagnosis or in establishing the prognosis of a case.

Dixon (1962),[2] avoiding the old terminology, has classified smallpox into nine clinical types. He purposely avoided the word "haemorrhagic", although recognizing the existence of this clinical entity, and termed it "fulminating" instead. Further, he recognized that the denisty of rash is not, by itself, of much diagnostic importance. Rightly, he introduced into his classification four types depending upon the nature and the evolution of lesions. Unfortunately, however, he listed three additional types based solely on the actual number of lesions on the body and called them by rather ambiguous terms, viz. the "discrete", "mild" and "abortive" types which have the inherent defect of being open to considerable subjective interpretation.

The Madras classification

From the author's clinical experience in caring for nearly 30 000 cases of smallpox during the last 25 years, two basic conclusions could be drawn:

1. That haemorrhagic smallpox is an entity, clinically and epidemiologically different from the non-haemorrhagic form and that the occurrence of haemorrhages into the skin and/or mucous membranes have definite prognostic importance.

2. That the number of lesions or the density of rash in the non-haemorrhagic varieties, is of secondary importance in assessing the prognosis and that it is the nature and the evolution of the lesions which determine the prognosis and not the number of lesions alone.

Based on these conclusions, a classification scheme was developed and has been used in Madras since 1961 with good results. Though it cannot be claimed to be perfect, it is a simple, workable and functional classification.

Four clinical varieties are defined in this classification, the "haemorrhagic", the "flat", the "ordinary", and the "modified". These may be further divided into 12 clinical types for more detailed studies. A brief clinical description of the four clinical varieties and the 12 clinical types is presented (Annex I).

The frequency of the clinical varieties

To determine the frequency and mortality rates of these different varieties, a detailed study was made of a series of 6893 consecutive cases of smallpox admitted to the Madras Infectious Disease Hospital during the last few years. Since, during the latter half of this period, a smallpox eradication programme was active, it is possible that it may have diminished the frequency of severe varieties of smallpox to some extent.

Table 1 presents the proportionate frequency and mortality rates of the different varieties and types among vaccinated and unvaccinated smallpox cases. As can be seen, the classification is made in such a way that the varieties and types are arranged in the descending order of their severity, thus helping in assessment of prognosis.

Further, the classification demonstrates that the density of rash per se has no prognostic significance, e.g., fatality rates were higher among "flat discrete" cases than among "ordinary confluent" cases and, similarly, "ordinary discrete" cases were more frequently fatal than "modified confluent" cases. Greater stress, therefore, is laid on the nature and the evolution of lesions than on their density.

Table 2 shows the frequency of the clinical varieties in each group according to vaccinal status. Forty per cent. of all cases that occurred in persons with evidence of both primary vaccination and successful revaccination were "modified" contrasted to 25% of cases vaccinated only in infancy and 1.1% of those in the unvaccinated.

Successful vaccination for the first time after exposure changes, to a certain extent, the course of the disease since 8.7% of these cases assured a modified course compared to only 1.7% in the unvaccinated.

"Flat" cases were less prevalent in the vaccinated than the unvaccinated, but for "haemorrhagic" cases the picture is different. This variety occurred in a slightly greater proportion amongst the vaccinated persons than the unvaccinated. Even in persons who had both primary vaccination and successful revaccination marks, 3.2% of the cases were "haemorrhagic" suggesting that even successful revaccination offers little protection against this variety.

Table 3 shows the frequency of the different clinical varieties with reference to sex. In the vaccinated, 4.3% of the female cases were haemorrhagic as against 2.4% for males. In the instance of "flat" cases, the proportion is slightly more among females whereas, in the unvaccinated, the proportionate frequency of "haemorrhagic" cases is the same but the "flat" cases were more frequent in females than in males.

Table 4 shows the frequency of clinical varieties with reference to age. Both in the vaccinated as well as the unvaccinated, the "haemorrhagic" variety was comparatively more frequent in adults beyond 14 years of age. This difference is more marked in the unvaccinated with 8% of the cases in the 15-44 year age-group, and 16.9% of the cases in the age-group 45 and above, occurring in this group.

As regards the "flat" variety, it is comparatively more common in young children and in older persons both in the vaccinated and unvaccinated, although the difference is more marked in the unvaccinated. With an increase in age in the vaccinated, the proportionate frequency of the "modified" cases decreases, probably as a result of waning immunity.

Table 5 shows the comparative frequency of the clinical varieties in pregnant women, non-pregnant women, and males of the same age-group, 15-44. In the vaccinated, 18.8% of cases in pregnant women were haemorrhagic contrasted to 2.3% of the male cases, and 2.2% of non-pregnant female cases. Similarly, in the unvaccinated, 31.7% of cases in pregnant women were haemorrhagic contrasted to 6.5% of cases in males and 5.4% in non-pregnant females. The proportion of "flat" cases was similarly more frequent in pregnant women.

Summary and conclusion

A clinical classification should be simple and should help in the diagnosis and prognosis of the disease. It has been found that the clinical variety of the disease may also have a bearing on the transmission pattern. Experience shows that haemorrhages occurring into the skin and/or mucous membranes in smallpox cases have definite prognostic significance and there is every justification for classifying haemorrhagic smallpox cases as a clinical entity. The density of rash, however, is not of much prognostic significance when compared to the nature and evolution of the lesions. The classification proposed and followed by the author since 1961 in Madras demonstrates these two basic principles.

From the frequency pattern, it is evident that in general the greater the vaccination immunity the less the severity of the disease as far as the non-haemorrhagic varieties are concerned. But in the case of the "haemorrhagic" variety, the frequency is not influenced by the vaccination status. Even in successfully revaccinated persons in whom there were no "flat" cases at all and among whom 50% of the cases were "modified", still 3.2% of the cases were haemorrhagic. This again suggests that the "haemorrhagic" variety is little influenced by vaccination.

In general, both vaccinated and unvaccinated females are more prone to experience the severe varieties of smallpox, especially the "haemorrhagic" form.

The haemorrhagic variety is far more frequent in adults beyond the age of 14 years both in the vaccinated and in the unvaccinated though the severe varieties of non-haemorrhagic smallpox were common in children. The frequency of the "modified" variety decreases with increasing age among the vaccinated.

On comparing the frequency of different varieties in the pregnant women with non-pregnant women and men of the same age-group, 15-44 years, it was found that the "haemorrhagic" variety of smallpox is nearly eight times more common in the vaccinated and 5-6 times more common in the unvaccinated, among pregnant women than non-pregnant women and men, respectively.

It is clear from these data that vaccination which offers protection against the severe varieties of non-haemorrhagic smallpox does not seem to offer the same amount of protection against the "haemorrhagic" variety. Further, women of the age-group 15-44, especially the pregnant, in spite of the vaccinial status, are far more susceptible to severe varieties of the disease especially the "haemorrhagic" form. Work is in progress to determine what factors in pregnant women may be responsible for this increase of susceptibility. It is presumed that the high level of cortisone in the blood of the pregnant women may have some role to play. Experiments are being conducted in monkeys to study the disease enhancing effect of cortisone. Recent studies of the "haemorrhagic" variety (Roberts et al., [3]; McKenzie et al., 1966[4]) showed that in this variety of smallpox there are blood coagulation defects which are not present in non-haemorrhagic forms, and that these changes are probably the result of intense viraemia or virus toxaemia. However, the reasons for the occurrence of such an intense viraemia in these cases is not known.

REFERENCES

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ANNEX I

CLINICAL DESCRIPTION OF THE INDIVIDUAL VARIETIES AND TYPES OF SMALLPOX

Variety I - haemorrhagic

These highly fatal cases are characterized by the occurrence of haemorrhages into the skin and/or mucous membranes at one stage or other in the course of the disease. The pre-eruptive stage is usually prolonged to four or five days associated with severe constitutional symptoms of severe headache, backache, vomiting, abdominal pain, pain in the chest, restlessness, pallor of the face and an anxious look. These toxic symptoms may continue after the onset of focal rash, if the patient survives to that stage. Haemorrhages may occur through any mucous surfaces. Sub-conjunctival haemorrhages are most common. Bleeding from the gums, epistaxis, haematemesis, haemoptysis, haematuria and vaginal bleeding in women may occur at any time. It is far more common in adults. Even successful vaccination does not seem to offer as much protection against this variety as it does against the non-haemorrhagic varieties. It is not uncommon to find a pregnant women dying of haemorrhagic smallpox in spite of her being protected by primary infant vaccination as well as recent successful vaccination within one year before exposure. The occurrence of this variety may depend upon hormonal disturbances in the host which may make the host more susceptible to infection as well as less resistant to the disease process.

Type 1 - early haemorrhagic

A highly toxic variety of smallpox with 100% fatality both in the vaccinated and the unvaccinated. The constitutional symptoms of the pre-eruptive stage are very severe; this stage is usually prolonged with the result that no frank rash may be seen before death although careful observation will usually show a few abortive papules on the abdomen. Haemorrhages into the skin and/or mucous membranes precede the rash on the skin. Characteristic are the flushed appearance, the restlessness, air hunger, heaviness in the chest, an abdominal discomfort tending to be colicky, facial pallor, excruciatingly severe backache, haemorrhages into the various mucous membranes and awareness of impending death till the end. Death usually occurs suddenly about the sixth to eighth day of disease.

In the absence of rash, these cases are likely to be misdiagnosed unless one watches carefully for the abortive papulo-vesicular lesions which appear on or about the fourth day. Smears from such lesions show sheets of elementary bodies of variola. It is not difficult to diagnose if one thinks of it. The restlessness, anxious look, flushed appearance and awareness of impending death are quite characteristic.

Type 2 - late haemorrhagic

The pre-eruptive stage may or may not be prolonged but the constitutional symptoms are very severe and continue to be present even after the occurrence of focal rash.

Haemorrhages into the skin and/or mucous surfaces may occur in any stage of the disease but usually they occur in the papulo-vesicular stage of rash. The lesions are usually flat with haemorrhages into the base of the lesions. The cases are febrile throughout with persistent constitutional symptoms. In a small number of cases, the lesions may mature and become pustular. Death occurs before the eighth or tenth day of the disease. Among survivors, haemorrhages stop gradually and the lesions, if flat, leave superficial scars but the convalescence is prolonged.

Annex I

Variety II - flat

This variety is called "flat" because the lesions flatten out and remain buried in the skin at the time they should project from the skin as round vesicles. The pre-eruptive stage is usually three or four days associated with the usual constitutional symptoms which are more severe in nature and which continue after the onset of the focal rash. The temperature continues to be elevated throughout. The focal lesions are exceedingly slow to mature and the vesicles at the usual time of maturation appear buried in the skin. There is very little fluid in the lesions. The majority have haemorrhages into the bases of the lesions (but not into the skin or mucous membranes). The lesions may have an erythematous areola. They do not evolve further than the vesicular stage. Frank pustules are rarely seen though it is not uncommon to find a few pustules on the dorsum of the hands and feet with flat lesions on other parts of the body. The distribution also may not be typically centrifugal and may not conform to the classical picture. There is no umbilication; the vesicles are not multilocular. Death occurs usually between the tenth to twelfth day of fever. Among survivors, the scarring is superficial.

Type 3 - flat confluent

The "flat confluent" type has all the general characteristics described above. The rash is confluent on the face and on the extensor aspects of the extremities. The patient is febrile and toxic throughout and invariably has respiratory involvement (? viral pneumonitis) which is not amenable to antibiotic therapy.

Type 4 - flat semi-confluent

This type is the same as Type 3 except that the rash is discrete on the extremities. The constitutional symptoms and mortality rate, especially in the unvaccinated, are the same whether they are Types 3, 4 or 5.

Type 5 - flat discrete

Nearly 30% of the "flat" cases in the vaccinated and 20% in the unvaccinated belong to this type. The case fatality rate is equally bad irrespective of the type.

Variety III - ordinary

This variety is called "ordinary" to indicate that this variety conforms to the usual description of a smallpox case. Patients experience the usual pre-eruptive stage of two or three days with constitutional symptoms of varying severity. There is a general abatement of symptoms at the time of onset of the focal rash though they may not completely disappear especially in the unvaccinated. The temperature tends to fall but may not reach normal. The lesions develop normally as macules and progress and evolve into papules, vesicles and pustules in 8-10 days after the onset of fever. The lesions present typical characteristics. They are round, projecting over the skin, deep set and can be rolled between the fingers. They are "in" the skin, multilocular in nature and present typical umbilication in the vesicular and vesiculo-pustular stage. Umbilication disappears in mature pustules. They are not usually surrounded by an erythematous areola. The distribution is usually centrifugal. Extensor surfaces and convexities are more involved than the flexors and concavities. Rickett's sign is positive in the majority of cases and Gaspirini's sign is positive in about 50% of cases. The lesions mature by about the thirteenth to sixteenth day and scabbing is complete by about the twenty-first to thirtieth day. Scabs separate leaving permanent deep scars; death in fatal cases occurs usually between the fourteenth to eighteenth day.

Annex I

Type 6 - ordinary confluent

The lesions on the face as well as the extensor surface of extremities are confluent. The temperature which tends to fall on about the fourth or fifth day rises again on the seventh day and continues to be elevated till the scabbing is complete. Sometimes in unvaccinated, the temperature remains elevated after scabbing is complete. This is associated with a bad prognosis.

Type 7 - ordinary semi-confluent

The rash is confluent on the face but discrete on the extremities. Secondary fever may occur in the vesicular and pustular stages but may be less severe and the temperature comes down as soon as the scabbing starts, though in unvaccinated children it may persist.

Type 8 - ordinary discrete

The rash is discrete all over. There may or may not be secondary fever, but the evolution of lesions will take the same time as Types 6 or 7. In some of these cases, the number of lesions may be as few as two or three but still these two or three may take 12 to 14 days to scab. The evolution of lesions is not modified in spite of the fact that the number of lesions are few.

Variety IV - modified

This variety of smallpox is so called because in these cases the characteristics and evolution of individual lesions are modified, as well as the constitutional symptoms. Though the majority may have comparatively few lesions, the number of lesions is not important as a criterion in judging the variety. These cases have the usual pre-eruptive stage which lasts about two or three days with moderate fever and headache. The temperature becomes normal by about the eighth day as soon as the focal rash appears completely and there is no secondary rise of temperature. The lesions which start as macules rapidly evolve into papules and vesicles and scab without going through the pustular stage. Sometimes they scab in the papular stage itself. Since in smallpox there is not much demarcation between the vesicular and pustular stages, it is empirically taken that any case of smallpox in which the whole rash has reached the scab stage by the tenth day of disease is modified, since normally by the tenth day pustules are maturing in the usual course of evolution. In the characteristics of the lesions there may also be modification. They may be more superficial than normal, though not so superficial as varicella; they may present pleomorphism with the rash appearing in crops. The scabs separate usually before the fourteenth day leaving very superficial scars which may not be permanent. None of these cases are ever fatal.

Type 9 - modified confluent

Though rare, this type does occur. The rash will be confluent on the face as well as the extremities but the rash reaches the scab stage before the tenth day. These cases are afebrile after the focal rash appears in spite of the density of the rash.

Type 10 - modified semi-confluent

This is a little more common than Type 9. The rash is confluent on the face and discrete on the extremities.

Annex I

Type 11 - modified discrete

Same as the above but the rash is discrete all over. Sometimes the number of lesions may be only one or two but still the rash is preceded by a typical prodromal fever. Though these cases may create difficulties in diagnosis, a careful clinical history along with careful appraisal of the depth of the lesions and the absence of typical pleomorphism will certainly help in diagnosis.

Type 12 - variola sine eruptione

This type is call thus because these cases do not present any rash on the skin. Diagnosis is difficult and certain only with laboratory confirmation. This type usually occurs in well-vaccinated persons but may occur rarely in the unvaccinated. They present a typical prodromal fever with the usual constitutional symptoms but develop no rash, though a few may complain of sore throat indicative of enanthem. However, these cases are most unlikely to be infective and hence are more of an academic interest.

TABLE 1. THE FREQUENCY OF THE CLINICAL VARIETIES AND TYPES, AND CASE FATALITY RATES WITH REFERENCE TO VACCINAL STATUS

Variety	In vaccinated		In unvaccinated		Type	In vaccinated		In unvaccinated	
	Frequency (%)	CFR	Frequency (%)	CFR		Frequency (%)	CFR	Frequency (%)	CFR
Haemorrhagic	3.3 (112)	93.7	2.4 (84)	96.4	Early haemorrhagic	1.4	100.0	0.7	100.0
					Late haemorrhagic	1.9	89.0	1.7	95.0
Flat	1.4 (46)	72.3	6.5 (230)	96.5	Flat confluent	0.7	87.0	4.1	98.6
					Flat semi-confluent	0.3	60.0	1.2	92.7
					Flat discrete	0.4	57.1	1.2	93.2
Ordinary	69.8 (2 355)	2.8	88.9 (3 126)	30.2	Ordinary confluent	4.4	23.5	22.8	61.9
					Ordinary semi-confluent	7.1	7.9	24.0	36.9
					Ordinary discrete	58.3	0.7	42.1	9.1
Modified	25.5 (862)		2.2 (78)		Modified confluent	0.1		0.025	
					Modified semi-confluent	0.5		0.025	
					Modified discrete	24.5		2.1	
					Variola sine eruptione	0.4		0.05	
Total	100.0 (3 375)		100.0 (3 518)						

( ) number of cases studied

TABLE 2. FREQUENCY OF CLINICAL VARIETY WITH REFERENCE TO VACCINIAL STATUS

Vaccinial status of smallpox cases	Number of cases	Variety I	Variety II	Variety III	Variety IV
Successfully vaccinated in infancy and successfully revaccinated	125	4	-	71	50
	(100.0)	(3.2)		(56.8)	(40.0)
Successful infantile vaccination only	3 250	108	46	2 284	812
	(100.0)	(3.3)	(1.4)	(70.3)	(25.0)
Never vaccinated or unsuccessfully vaccinated (no scars)	3 026	81	202	2 708	35
	(100.0)	(2.7)	(6.7)	(89.5)	(1.1)
Vaccinated successfully only after exposure	492	3	28	418	43
	(100.0)	(0.6)	(5.7)	(85.0)	(8.7)

( ) percentage of total in group

TABLE 3. FREQUENCY OF CLINICAL VARIETIES WITH REFERENCE TO SEX AND VACCINIAL STATUS

( ) percentage to the total in that group

Vaccinial status	Sex	Number of cases	Variety I	Variety II	Variety III	Variety IV
Vaccinated	Males	1 800	44	17	1 266	473
		(100.0)	(2.4)	(1.0)	(70.3)	(26.3)
	Females	1 575	68	29	1 089	389
		(100.0)	(4.3)	(1.8)	(69.1)	(24.7)
Unvaccinated	Males	1 734	46	91	1 560	37
		(100.0)	(2.1)	(5.3)	(90.0)	(2.1)
	Females	1 784	38	139	1 566	41
		(100.0)	(21)	(7.8)	(87.8)	(2.3)

TABLE 4. FREQUENCY OF CLINICAL VARIETY WITH REFERENCE AGE AND VACCINIAL STATUS

Vaccinial status	Age	Number of cases	Variety I	Variety II	Variety III	Variety IV
Vaccinated	0-4	94 (100.0)	1 (1.1)	5 (5.3)	54 (57.4)	34 (36.2)
	5-14	387 (100.0)	7 (1.8)	2 (0.5)	229 (59.2)	149 (38.5)
	15-44	2 677 (100.0)	96 (3.6)	32 (1.2)	1 903 (71.1)	646 (24.1)
	45+	217 (100.0)	8 (3.7)	7 (3.2)	169 (77.9)	33 (15.2)
Unvaccinated	0-4	2 077 (100.0)	23 (1.1)	168 (8.1)	1 825 (87.9)	61 (2.9)
	5-14	851 (100.0)	8 (0.9)	33 (3.9)	802 (94.3)	8 (0.9)
	15-44	525 (100.0)	42 (8.0)	22 (4.2)	453 (86.3)	8 (1.5)
	45+	65 (100.0)	11 (16.9)	7 (10.8)	46 (70.8)	1 (1.5)

( ) percentage of total in group

TABLE 5. FREQUENCY OF CLINICAL VARIETIES WITH REFERENCE TO PREGNANCY, THE NON-PREGNANT AND MALES OF THE SAME AGE-GROUP, 15-44 YEARS

	Vaccinial status	Number of cases	Variety I	Variety II	Variety III	Variety IV
Pregnant 15-44 years	Unvaccinated	41 (100.0)	13 (31.7)	2 (4.9)	26 (63.4)	-
	Vaccinated	213 (100.0)	40 (18.8)	8 (3.7)	132 (62.0)	33 (15.5)
	Total	254 (100.0)	53 (20.9)	10 (3.9)	158 (62.2)	33 (13.0)
Non-pregnant female 15-44 years	Unvaccinated	239 (100.0)	13 (5.4)	15 (6.3)	207 (86.6)	4 (1.7)
	Vaccinated	989 (100.0)	22 (2.2)	14 (1.4)	708 (71.6)	245 (24.8)
	Total	1 228 (100.0)	35 (2.8)	29 (2.4)	915 (74.5)	249 (20.3)
Males 15-44 years	Unvaccinated	245 (100.0)	16 (6.5)	5 (2.0)	220 (89.9)	4 (1.6)
	Vaccinated	1 475 (100.0)	34 (2.3)	10 (0.7)	1 063 (72.1)	368 (24.9)
	Total	1 720 (100.0)	50 (2.9)	15 (0.9)	1 283 (74.6)	372 (21.6)