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EPIDEMIOLOGICAL STUDY OF ABNORMAL BCG SCARS AMONG PRIMARY AND HIGH SCHOOL PUPILS IN TAIWAN (CHINA)[1)]

Part 2. Physical Characteristics of Abnormal BCG Scars

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MATERIALS AND METHODS

Study population and methods were the same to those of Part 1 of this report. Out of 12,313 pupils of primary and high schools randomly selected from the third, fifth, eighth and eleventh grades, 2,799 showed abnormal BCG scars. Physical characteristics of these abnormal scars were observed by one and the same dermatologist, and the results were as follows.

RESULTS

Physical characteristics of abnormal BCG scars

Colour

Keloid were often pinkish (67.3%), some of them brownish (30.0%) and only exceptionally whitish or normal (1.3% and 1.1%, respectively). The majority of atrophic scars had either brownish or normal skin colour and only a few were whitish or pinkish. The colour of hypertrophic scars was somewhat in between of the other two types of scars; a little more than one third were pinkish and the rest either brownish, whitish or normal in about the same proportion (around 20% each).

Hardness

In general, a relatively high proportion of keloids were hard (43.2%), while the great majority of atrophic scars were soft (94.0%) and the great majority of hypertrophic scars moderate (90.0%). However, as many as 55.9% of keloids had a moderate hardness and only exceptionally some were soft (0.9%).

Size

As shown in Table 5, abnormal BCG scars were larger than normal scars, and among the three types of abnormal scars, keloids were the largest. All BCG scars, including both normal and abnormal, were large among the high school pupils than the primary school pupils and the difference in mean size between these two groups was greater for abnormal scars than for normal scars, being the greatest for keloids. From these observations, it can be said that keloids are in general larger than the other types of scars, both normal and abnormal BCG scars increase in size as the children grow up and the rate of growth is faster in keloids than in other types of abnormal BCG scars.

Characteristics of keloid

Table 6 shows how often the five characteristics set as disgnostic criteria in this study appear, either alone or in combination of one or more, in the 544 keloids observed in 470 pupils. They are summarized as follows:

One	Two	Three	Four	Five	Total
359	160	18	7	0	544
66.0%	29.4%	3.3%	1.3%	0%	100.0%

Among the 359 keloids with one characteristic as a diagnostic criterion, the great majority had "projections like crab claws", which were followed by "larger than the original scar" and "teleangiectasis and tense red

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Table 5. Size of Various Types of Abnormal BCG Scars in Primary and High School Pupils as Expressed by Mean Size, and Percentage of Scars 15 mm and Above

Pupils	Normal BCG scar	Abnormal BCG scars			
		Atrophic	Hypertrophic	Keloid	Total
Mean size (mm)					
Primary school	4.81±2.00	5.42±1.48	6.29±2.04	10.62±4.74	6.77±2.92
High school	6.91±2.97	7.60±2.04	9.13±3.22	14.37±5.93	10.03±4.35
Percentage of size 15 mm and above					
Primary school	0%	0%	0%	14.7%	2.3%
High school	1.5%	1.4%	5.7%	42.8%	9.5%

Table 6. Distribution of Keloids by Characteristics of Keloid

Characteristics or combination of characteristics	Keloids among primary school		Keloids among high school		Total	
	Pupils		Pupils		Pupils	
	No.	%	No.	%	No.	%
One characteristic						
Projections like crab claws	62	81.6	249	88.0	311	86.6
Larger than original scar	7	9.2	24	8.5	31	8.6
Teleangiectasis and tense red margin	7	9.2	10	3.5	17	4.7
Still growing	0	0	0	0	0	0
Itchy or painful sensation	0	0	0	0	0	0
Total	76	100.0	283	100.0	359	100.0
Combination of two characteristics						
P and L	10	32.3	56	43.4	66	41.2
P and T	12	38.7	19	14.7	31	19.4
P and G	2	6.5	4	3.1	6	3.8
P and I	5	16.1	40	31.0	45	28.1
L and T	2	6.5	1	0.8	3	1.9
L and G	0	0	1	0.8	1	0.6
L and I	0	0	6	4.7	6	3.8
T and I	0	0	2	1.6	2	1.3
Total	31	100.1	129	100.1	160	100.1
Combination of three characteristics						
P, L and T	1	16.7	2	16.7	3	16.7
P, L and I	2	33.3	4	33.3	6	33.3
P, L and G	0	0	2	16.7	2	11.1
P, G and I	0	0	1	8.3	1	5.6
P, T and I	3	50.0	2	16.7	5	27.8
T, G and I	0	0	1	8.3	1	5.6
Total	6	100.0	12	100.0	18	100.1
Combination of four characteristics						
P, L, G and I	1	33.3	3	75.0	4	57.1
P, T, G and I	1	33.3	1	25.0	2	28.6
L, T, G and I	1	33.3	0	0	1	14.3
Total	3	99.9	4	100.0	7	100.0

P: Projections like crab claws; L: Larger than original scar; T: Teleangiectasis and tense red margin; G: Still growing; I: Itochy or painful sensation.

margin". No diagnosis of keloids was made on the basis of "still growing" or "itchy or painful sensation", which is by itself rather subjective in nature. "Teleangiectasis and tense red margin" is more frequently seen in keloids among primary school pupils than high school pupils.

Among the 160 keloids with a combination of two characteristics and also among the 18 with combination of three, "projections like crab claws" were again most frequently seen in combination with others, followed by "larger than the original scar" and "teleangiectasis and tense red margin". Again combinations including teleangiectasis were more frequently seen in keloids among primary school pupils. This may imply that teleangiectasis is more commonly seen in fresh keloids and tends to disappear as time goes on.

Smallpox scars

Correlation between smallpox scars and BCG scars in the same persons by normal and abnormal scar is shown in Table 7. Of the total of 10,001 persons with BCG scars, 50 or 0.5% did not have smallpox scars. Of the total of 9,961 with both BCG and smallpox scars, only 21 or 0.21% had abnormal smallpox scars. Ten of them belong to the group with abnormal BCG scars. Thus, the proportion with abnormal smallpox scars was 0.37% for the former group and 0.15% for the latter group. The difference, while samll, is on the border of statistical significance.

DISCUSSION

Recently more and more people have raised concern over the ugly scars resulting form BCG vaccination. However, it is not known whether this is because people are becoming more cosmetically minded or because the actual incidence of disfiguring abnormal BCG scars is increasing. It is true, however, that detailed information on this subject is extremely scarce. These facts had prompted the authors to conduct this study in Taiwan in 1967～1968.

There are only a few reports available concerning this subject. As stated above, Hsing (1) reported an incidence of 10% of keloid formation among school children in Taiwan. The WHO Western Pacific Regional Tuberculosis Advisory Team (2) also reported a high incidence of keloids in a trial of BCG vaccination among school children conducted in Cebu City, the Philippines ; the incidence rate of keloid one year after vaccination was 22.9% and 38.8%, respectively, among tuberculin non-reactors without and with old BCG scars, and it was even higher among tuberculin reactors, 40.4% on the whole. However, two years after vaccination, all of these rates decreased to 13.7%, 30.2% and 33.3%, respectively. The diagnostic criteria used for keloid is not clear in the report, but judging from the fact that the rate decreased after one year, possibly hypertrophic scars were included in keloids because genuine keloids very rarely involute.

In another study (2) also from Cebu City, which was primarily designed to compare the potency of liquid and freeze-dried BCG vaccine, an incidence rate of keloid of 26.2% and 27.7%, respectively, was reported for both vaccine groups after 13 months. In addition, they also reported a finding of "slightly elevated scars", 12.2% and 12.2%, respectively, and "slightly depressed scars", 1.3% and 0.8%, respectively, for both vaccine groups. The latter, i.e., slightly depressed scars, may correspond to atrophic scars in the present study with a similar rate. However, it is difficult to know what proportion of those reported as keloids and slightly elevated scars corresponds to keloids and hypertrophic scars as defined in the present study.

Egsmose (3) reported from Kenya the following incidence rates of keloid formation in a study on the

Table 7. Normal and Abnormal Smallpox Vaccination Scars by Normality of BCG Scars

BCG scars	Smallpox scars							
	Normal		Abnormal		Sub-total		None	Total
	No.	%	No.	%	No.	%		
Normal	7,176	99.85	11	0.15	7,187	100.00	25	7,212
Abnormal	2,764	99.63	10	0.37	2,774	100.00	25	2,799
Total	9,940	99.79	21	0.21	9,961	100.00	50	10,011

feasibility to vaccinating tuberculin positive reactors :

Vaccine used	Non-reactors	Reactors
Japanese freeze-dried	1.1%	5.6%
Pasteur freeze-dried	6.0%	7.0%
Glaxo freezed-dried	3.7%	14.6%

The rates were higher among reactors than among non-reactors. Although the rates among the non-reactors seem to be close to those of the present study, the following difference must be noted: Egsmose's study was dealing with the incidence of keloids at 9 months after vaccination, while the present study is concerned with the prevalence of keloids among those who had received BCG vaccination at varying time points spreading over between 2 and 15 years. Furthermore, the definition of keloid in his study was simply "a hard protuberant mass in the scar, which is a cosmetic blemish", and nothing was mentioned about hypertrophic scar.

In a later study of BCG vaccination of tuberculin reactors, Egsmose (4) observed 4 cases with keloid formation out of 1936 consecutive examinations, or 0.2%, and stated that "none could be described as a serious cosmetic disadvantage". In this study, vaccination was made at the dorsal aspect of the left forearm and observation was made between 6 to 24 months after vaccination, the majority after 12 months. This incidence rate of 0.2% of keloid formation is definitely lower than his previous observation of 5.6%. He attributed this discrepancy in findings to the different sites of vaccination in these two studies and explained that "the short sleeves of the school uniform covered the shoulder but not the forearm, and exposure to sunlight is therefore different for the two vaccination sites. The almost daily direct sunlight stimulates healing of the BCG process".

After reviewing the frequencies of keloid formation between the Philippines and Kenya, ten Dam (5) stated that such a striking difference may be partly explained by possible difference in interpretation and the criteria used. In none of the above mentioned studies, hypertrophic scars were reported as a type of abnormal BCG scars, but it is highly probable that some of the large hypertrophic scars were regarded as keloids. In a study of children in Bangkok, Thailand, by the National Tuberculosis Programme (6), distinction was made between these two types of abnormal BCG scars. It was reported that two cases of keloid (1.6%) were found in 126 children who had been veccinated only once and that hypertrophic scars were rather prevalent, 14～15 %.

Histologically it is possible to differentiate these two types of abnormal BCG scars easily, but clinically it depends very much on the criteria employed to differentiate them with a reasonable accuracy. In the Bangkok study (6) keloid was defined as "an outgrowth over the site of the original lesion, with a margin steeply elevated above the normal skin, with a smooth and shiny surface and teleangiectasis", while hypertrophic scars were subdivided into "slightly hypertrophic" and "protruding hypertrophic" by degree of protrusion. Thus the protruding hypertrophic scar was defined as "protruding markedly over the normal skin surface, growth being limited to the traumatized area, firm upon palpation, without teleangiectasis". It is noted that these definitions are very similar to those employed in the present study; namely, "the growth beyond the traumatized area" and "a margin steeply elevated above the normal skin with teleangiectasis" correspond well to the second and third criteria of keloid, respectively, of the present study, i.e., "larger than the original scar" and "teleangiectasis and tense red margin". However, the first criterion, i.e., "having projections like crab claws" was missing in the Bangkok study, which seems to the authors to be the most important one because it was most commonly found.

Among the five characteristics of keloids employed in the present study, two are rather subjective ones, i.e., "still growing" and "itchy or painful sensation", which must be based on the pupils' own statement. However, it must be noted that none of these two was used by itself for diagnosis of keloids and instead they were always found in combination with other conditions which were derived from the investigator's own observation. Size was not used as a diagnostic criterion in this study because keloid can be very large but also be very small as Andrews et al. (7) pertinently described: "sometimes keloids are as tiny as pinheads and again one may be as large as an orange". In this study some keloids were as small as 2～3 mm and the largest was 42

mm in diameter. On the other hand, two normal scars were as large as 30 mm. However, in general, keloids are larger, harder and more or less pinkish; atrophic scars are smaller, brownish or whitish, and moderate in hardness and size.

The chance of having an abnormal scar among the pupils with one BCG scar was approximately one in five irrespective of grade, and it became doubled as the number of BCG scars in the same person increased to two, probably because each of the two scars had the equal chance of becoming abnormal, or the second vaccination may have stimulated the old scar to become abnormal or vice versa. It was also proved that in pupils with multiple scars the chance of having all scars abnormal is higher than expected and furthermore there were significantly more paired scars of the same type than can be accounted for by chance. In the Bangkok study (6) it was also observed that a child with a scar of one type tended to show another scar of the same type more often than might have been expected. This fact, together with the finding of a slightly higher rate of pupils with abnormal smallpox scars among those with abnormal than among those with normal BCG scars, may allow us to assume that a certain proportion of children have a strong hereditary tendency to develop scars of a given type, keloids for example, upon an appropriate stimulus and that BCG vaccination provides such a stimulus so that in this group two BCG vaccinations would always produce paired keloids. This is equivalent to say that there are two populations of children, one always gets keloid on BCG vaccination and the other gets keloid more or less at random.

Preponderance of abnormal BCG scars, especially keloids, among females also speaks for existence of inherent factors in causations of such abnormal BCG scars. The higher ratio of keloids among the higher graders, however, should not be interpreted as an age-specific predisposion to keloid but it is most probably due to a longer lapse of time after vaccination in older pupils, because formation of keloids is rather a slow process and often requires years to maturate. There may be a racial difference in keloid formation after BCG vaccination, but so far information has been scarce, and if any, the real difference has often been masked by different diagnostic criteria employed so that no comparison between different races can be made at this stage. For this reason, international, cooperative studies with the same methods and criteria are strongly recommended.

On the basis of the above findings, the authors propose that BCG vaccination be better avoided for those who show an abnormal scar resulting from the previous BCG vaccination. The authors of the Cebu study (2) recommended that revaccination be avoided whenever possible, because the presence of an old BCG scar could enhance the development of keloid after BCG vaccination and also because the value of revaccination was still doubtful. However, the present authors would take a rather reserved attitude in respect to a complete abolishment of the revaccination scheme because, before doing so, many factors other than the mere chance of developing abnormal BCG scars should be taken into consideration, such as the effectiveness of revaccination, the need of protection for the groups of children concerned, the time intervals, etc.

Inadequate techniques in vaccination, such as too deep an injection or inadequate site of vaccination, may favour the formation of abnormal BCG scars. In this study, attempts were made to investigate whether such a relationship exists, but no conclusion could be made. Again no conclusion was drawn from the investigation on the site of vaccination, because very few pupils were found to have BCG scars at an inadequate site (If a BCG scar is located within the left deltoid region, it is considered adequate; otherwise inadequate). Therefore, it is left to the future controlled study to prove such a relationship, in which different sites can be selected and vaccination made either too deeply or too superficially and even different doses of BCG vaccine can be applied. However, as mentioned above, Egsmose (4) has demonstrated that vaccination made at the dorsal aspect of the forearm was less likely to result in keloid formation. The Bangkok study (6) also found that the scars in the acromion region appeared to show a higher prevalance of protruding hyportrophic scars and a greater mean size than in the lower vaccination site as it was expected that BCG lesions would be subject to a greater irritation by mechanical stimulation on the tense skin there.

But why do keloids or abnormal scars appear more frequently from BCG vaccination and less often from smallpox vaccination? The most probable reason for this difference could be that BCG ulcers are tuberculous tissue changes, the healing of which tends to proctract whereas smallpox ulcers follow an acute course and heal

completely in a matter of two or three weeks. Whether such a protracted healing of BCG ulcers leads to formation of keloids or other types of abnormal scars more frequently than smallpox vaccination or whether the very nature of mycobacteria is responsible for such a phenomenon is difficult to determine from this study. But this finding of different risks of forming keloids or abnormal scars between these two types of vaccination may have provided some clues to the understanding of pathogenesis of keloids and other types of abnormal scars resulting from BCG vaccination. As mentioned above, Egsmose (6) attributed the lower incidence of keloids formation from BCG vaccination at the forearm to the accelerated healing of ulcers due to more exposure to sunlight. In other words, he assumed that more frequent keloid formation at the shoulder was due to protracted healing of ulcers because of less exposure to sunlight.

What is the practical implication of the frequency of abnormal BCG scars, especially keloids, as revealed by this study? Certainly, keloids were not as frequent as Hsing (1) pointed out, i.e., 10% among primary school pupils in Taiwan; instead, it was 4.7% as a whole and only 1.6% among the third grade and 3.4% among the fifth grade pupils. However, more important is the potentiality of keloids to increase with age. Thus, the frequency increased to 6.0% and 6.7%, respectively, at the eighth and eleventh grade. It is not known whether it would increase further beyond the high school ages, but it is certainly disturbing from the cosmetic point of view that keloids are more frequently seen among females than males (8.0% and 5.2% respectively at the eleventh grade). It is quite up to subjective judgement whether the prevalence ratio of keloids at such a level is serious enough, and again the judgement may differ at different stages of socio-economic development of the country.

The fact remains, however, that although the living standard of people in Taiwan has been rising rapidly as judged by the increase in per capital income and although several years have passed since Hsing's warning in 1963 (1), BCG vaccination in Taiwan has not yet reached the point when "people refuse to be vaccinated". Instead, there are even signs of its increasing popularity; for example, the coverage of BCG vaccination of infants, which is given simultaneously with smallpox vaccination, has never fallen below 80% of the total infant population each year since such a practice was introduced in 1965. Neverthless, in view of the disfiguring appearance and tumour-like growth of keloids and also in view of even higher frequency of hypertrophic scars, of which some are large enough to cause worries too, this problem of abnormal BCG scars deserves serious attention of the authorities concerned, and efforts should be made to reduce their incidence. For this reason, further planned studies on this problem are strongly advocated.

SUMMARY

An epidemiological survey was made of abnormal BCG scars among pupils at the third and fifth grade of primary schools and the eighth and eleventh grade of high schools in the northern part of Taiwan. The overall ratio of pupils with abnormal BCG scars was 28.0%; 4.7% with keloids, 22.2% with hypertrophic scars and 1.1% with atrophic scars. The frequency of keloids increased with age from 1.6% at the third grade to 6.7% at the eleventh grade and it was more frequent among females than males, 8.0% as compared with 5.2%, at the eleventh grade. Each type of abnormal BCG scars is more likely to appear in combination of the same type than would be expected if multiple vaccinations are given. Therefore, it is recommended that revaccination be avoided in case the first BCG scar is found to be abnormal. "Projections like crab claws", "the mass being larger than the original scars" and "teleangiectasis and tense red margin" are the main characteristics of keloids, which are missing in hypertrophic scars, and considered to be useful diagnostic criteria. Although the frequency of abnormal BCG scars as found in this study is not alarming enough to endanger the implementation of BCG programme in Taiwan at present, attention should be given to the potential danger of this problem and efforts should be made to reduce the frequency of abnormal BCG scars by finding possible means to prevent their formation.

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Correction

Kindly correct the error found in Vol.51, No.6, Table 4 on Page 244 as follows:

Under the heading "**No. of pupils**", in the first colum "**No.**", in the 5th line from the top——

For "**22**" read "**222**".