TUBERCLES OF THE CHOROID

BY

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[WITH COLOUR PLATE]

It has long been known that careful examination of the fundus oculi in cases of miliary tuberculosis and tuberculous meningitis may reveal tubercles of the choroid. The concentration of cases of this disease and the prolongation of life which has resulted from streptomycin therapy have provided the opportunity of studying these choroidal lesions and of observing their natural history. In this paper we discuss the frequency with which we were able to find tubercles of the choroid, describe their natural history, and report the findings of similar lesions in cases of tuberculosis in which there was no evidence of miliary spread or of meningitis.

Historical

It seems that Gueneau de Mussy (1830) was the first to recognize choroidal tubercles in miliary tuberculosis. Jaeger (1855) gave the first anatomical demonstration of these lesions. Manz (1858) described the detailed histology of a choroidal tubercle in a girl aged 15 who died of miliary tuberculosis. Fraenkel (1867) was the first to demonstrate them with the ophthalmoscope, though Von Graefe and Leber (1868) claimed that they were the first to demonstrate them with this instrument. They described the ophthalmoscopic appearance in detail. Cohnheim (1867) gave a detailed description of the necropsy on seven cases, and produced choroidal tubercles experimentally (with miliary tuberculosis) by injecting guinea-pigs with tuberculous material.

Various writers (Fraenkel, 1869; Weiss, 1877; Marple, 1912; Groenouw, 1920; Lotin, 1924) suggest that choroidal tubercles may develop in a few hours. This seems to be extremely unlikely, and the statement is almost certainly accounted for by incomplete initial examination. Bouchut (1869), Fraenkel (1869), and Weiss (1877) emphasized the value in diagnosis of finding choroidal tubercles. Hoeve (1925), Bollack *et al.* (1927), Mayrhofer (1935), and Baldenweck *et al.* (1938) describe cases in which the diagnosis of miliary tuberculosis was established by finding tubercles of the choroid. The literature was reviewed by Von Graefe and Leber (1868), Weiss (1877), Carpenter and Stephenson (1905), Bredeck (1916), Groenouw (1920), Bollack *et al.* (1927), and Paton (1932).

The frequency with which various writers found choroidal tubercles is tabulated below. In many papers it is very difficult to determine whether the cases referred to were meningitis only, miliary tuberculosis only, or a combination of these. The great majority were cases of miliary tuberculosis with or without meningitis. In cases referred

to as meningitis only, the absence of post-mortem evidence that there was no miliary spread makes the accurate designation of these cases impossible: for, as mentioned below, careful histological examination not infrequently reveals miliary tuberculosis which on x-ray examination had not been evident.

TABLE I

	No. of Cases	No. of Cases in which Choroidal Tubercles were Found
Koch (1913)	60	8
Koplik (1907)	46	9
Garlick (1879)	26	1
Cohnheim (1867)	18	18
Groenouw (1920)*	225	54
Heinzel (1875)	41	0
Litten (1877)	52	39
Bredeck (1916)	11	2
Tooke (1915-16)	73	7
Moore (1922)	33	10
Carpenter and Stephenson (1905) ..	42	21
Marple (1912)	13	13
McDermott <i>et al.</i> (1947)	13	2
Debré <i>et al.</i> (1947)	84	22
Total	737	206 (28%)

* Quoting Stricker, 1876; Weissenfels, 1881; Bock, 1883; Money, 1883; Neskovic, 1884; Demme, 1888; Rheinhold, 1891; and Grüning, 1901.

A recent textbook (Doggart, 1947) merely states that "choroidal tubercles are visible in many cases of tuberculous meningitis."

The Clinical Material

Between January, 1947, and May, 1948, 65 cases of miliary tuberculosis and tuberculous meningitis in patients under the age of 14 were admitted to the Children's Hospital, Sheffield. Ten of these cases are excluded from the series to be discussed—four because the fundi were not examined, three on account of some doubt whether or not choroidal tubercles were seen, two because it was impossible to classify the cases owing to lack of x-ray and necropsy examination, and one because pneumococcal meningitis in a case of miliary tuberculosis masked the possible presence of tuberculous meningitis. The difficulty in some of these cases arose because the child was moribund on admission.

By the courtesy of Professor E. J. Wayne and Professor C. H. Stuart Harris we were able to examine the fundi of five unselected adults suffering from miliary tuberculosis or meningitis, and these are included in the series.

Four additional cases of pulmonary tuberculosis in children are discussed because of the finding of choroidal

tubercles without evidence of miliary spread or meningitis. These are not included in the series of 60 cases given in Table II.

Technique of Examination

It is obvious that the accurate examination of the fundi of infants and small children is a matter of considerable difficulty, and requires much patience and experience. The irritability occasioned by meningitis may make the examination particularly difficult. The pupils in all cases were dilated by 1% homatropine, and a sedative drug such as chloral, 1½ gr. (0.1 g.) per year of age, was used where necessary. The average time occupied for one examination of the fundi of a small child is about half an hour.

In almost all the children the fundi were examined repeatedly, but in view of the difficulties it is possible that in some cases choroidal tubercles were present but not detected. We feel, however, that in view of the care with which the examinations were carried out the number missed is likely to be small. It is certainly possible that histological examination would reveal tubercles which were too small to be detected by the ophthalmoscope.

TABLE II.—Frequency of Choroidal Tubercles in the Series

	No. of Cases	No. of Cases in which Choroidal Tubercles were Found
Miliary tuberculosis	14	7
" with meningitis	28	18
Meningitis	18	1
Total	60	26

It will be seen from Table II that choroidal tubercles were found in 25 (60%) out of 42 cases of miliary tuberculosis with or without meningitis, and in only one case of meningitis in which there was no miliary spread. This last case was one of chronic tuberculous caries of the spine with terminal meningitis. Careful histological examination of the organs did not reveal miliary lesions. Of the five adults seen, all suffering from miliary tuberculosis with meningitis, choroidal tubercles were found in three.

That post-mortem examination, especially histological section, is necessary to exclude miliary spread is shown by the fact that in nine of our cases of meningitis in which x-ray examination failed to indicate miliary infection the necropsy revealed miliary lesions in the lungs, in six of these only on histological examination. Our figures for the cases of meningitis without miliary spread may not be quite accurate, as five of the 18 patients are still alive (though two have been observed for more than three months) and in three of the 13 fatal cases no post-mortem examination was possible. Therefore it may be that some of these eight cases should have been included in the group of cases of miliary tuberculosis with meningitis.

It is noteworthy that Sir Frederick Still (1927) said: "Tubercles of the choroid are rarely found in tuberculous meningitis if uncomplicated by miliary tuberculosis, whereas they are found in the majority of cases of miliary tuberculosis."

It is interesting that, whereas choroidal tubercles were found in 24 out of 33 cases in which there was x-ray evidence of miliary tuberculosis, they were found in only 1 out of 9 cases in which the miliary lesions in the lung were so small or non-opaque that they could only be discovered at necropsy. The significance of this observation is not clear.

The frequency of choroidal tubercles in the cases of miliary tuberculosis emphasizes the importance and value of a thorough examination of the fundi in all cases of possible miliary tuberculosis or meningitis. In some of the cases

of meningitis in the series the finding of choroidal tubercles enabled a definite diagnosis to be made before an x-ray photograph of the chest was available and before a lumbar puncture had been performed.

In almost all cases the choroidal tubercles were found at the time of the first or second examination. Several writers have suggested that they are found only in the terminal phase of the illness. Our experience does not confirm that suggestion.

In only one case did we observe the appearance of choroidal tubercles during the course of streptomycin treatment. In view of the unsatisfactory response of some cases to streptomycin there seems to be no reason why this should not happen, but it must be remembered that the difficulty of full examination of the fundi of an infant makes it very easy to miss choroidal tubercles at the time of the first one or two examinations. Their discovery may well be explained by an inadequate search previously.

Description of the Choroidal Tubercle

In the early stage (Plate, Fig. 1) the choroidal tubercle appears as a rounded pale-yellow area with a matt surface and an indefinite edge merging into the red background of the choroid. It does not appear to be elevated. There may be only one tubercle, but usually there are several. The largest number observed by us in one eye was ten. The majority are one or two disk-breadths from the disk. The size is usually one-quarter to three-quarters that of the disk, but it is sometimes slightly larger than the disk. It is unconnected with the retinal vessels. It may be traversed by vessels, and if so they are apparently normal.

The histological appearance of the tubercle has been well described by many writers (Manz, 1858; Cohnheim, 1867; Bouchut, 1869; Weiss, 1877; Haab, 1879; Carpenter and Stephenson, 1905; Petrovic, 1926; Bollack *et al.*, 1927; Penman and Wolff, 1933; Tooke, 1936; Baldenweck *et al.*, 1938). Tooke (1936) draws attention to the absence of involvement of the vaginal space and optic nerve sheath, and considers that this is good evidence that choroidal tubercles arise from miliary spread and not by extension from meningitis.

There is swelling of the neighbouring choroid, with destruction of the stroma and infiltration with round cells, endothelial cells, and giant cells. Tubercle bacilli have been found in the lesions in large numbers. The retina is rarely involved, the tubercle being strictly limited to the choroid, but the retina may be thickened and show round-cell infiltration (Penman and Wolff, 1933). The retina is often involved by so-called conglomerate tubercles (Groenouw, 1920; Petrovic, 1926; Groenval, 1933; Balza and Mosto, 1935; Harlowe, 1946).

The Natural History of the Choroidal Tubercle

We have found very little reference in the literature to changes in the choroidal tubercle. Von Graefe and Leber (1868), Fraenkel (1869), and Groenouw (1920) all mention the increase in size which can be observed by repeated observation. Cohnheim (1867), Von Graefe and Leber (1868), and Fraenkel (1869) describe the paling of the lesion which develops with its increase in size. Marple (1912) shows a good picture of an obviously old tubercle. Barlow (1910) says: "Choroidal tubercles may be observed in different stages of development in different parts of the fundus. They begin as minute round dots which gradually become more opaque in their centre." Very little reference has been made to pigmentation. Von Graefe and Leber (1868) mention the occurrence of pigmentation in large tubercles. Debré *et al.* (1947) say that "they gradually heal or disappear, leaving residual pigmentation only." They go

on to say that new choroidal tubercles may appear during the course of streptomycin therapy, and may serve as the only indication that all is not well. Lotin (1924) says that pigmentation sometimes occurs in these tubercles and that a chronic course is not uncommon in tubercles of the choroid.

The relative effectiveness of streptomycin treatment has enabled us to observe the changes which occur in choroidal tubercles over a period of several months. We have not seen any tubercles disappear during treatment, and in view of their pathology it would seem unlikely that this would happen. In some cases the tubercles may remain unchanged for some weeks. The possible prognostic significance of the absence of changes in the tubercles is mentioned below.

In at least 20 cases we observed well-defined and definite changes. The area occupied by the tubercle becomes larger and paler and the outline more distinct. Fine dots of pigment appear in and around the pale area (Fig. 2). This change is usually noted within eight weeks of starting treatment.

Following this intermediate stage the tubercle becomes paler still, until finally it becomes parchment-white, with a well-defined sharp edge, with heavy black pigment in and particularly around the lesion. There may also be a paling of the red choroid in the area immediately around the tubercle (Figs. 3-6). These changes may be complete in 12 to 14 weeks. We think that this parchment-white scar with a well-defined edge and heavy pigmentation may represent the healed tubercle. We have seen incomplete pictures of this several times but the final parchment-white stage in only five cases. One was a case of miliary tuberculosis with meningitis which responded well to four months' streptomycin treatment. The girl had a solitary choroidal tubercle, and we observed in it all the changes from the earliest to the final stage. She is now perfectly well, four months after the cessation of treatment. In another case, discussed below, we noted the same changes occur in a solitary choroidal tubercle in a girl with a tuberculous knee without miliary tuberculosis or meningitis. In another case one choroidal tubercle underwent these changes during the course of four months' streptomycin treatment (Fig. 3), while other tubercles, about a dozen in number, never progressed beyond the early intermediate stage: she died. In another case, admitted with a five-months history of miliary tuberculosis, one choroidal tubercle was found in this late stage, while others were found in the early and intermediate stages. The different age of these tubercles may well be due to a continued discharge of tubercle bacilli from the primary focus. In yet another case we observed a choroidal tubercle in the final stage in a child with a primary complex with no evidence of miliary infection or of meningitis. In this case the tubercle had not been observed in the earlier stages. This case is also discussed below.

Possible Prognostic Value of Changes in Choroidal Tubercles

We have seen too few cases and observed them for too short a period of time to be able to make any definite statement about the prognostic value of the changes we have described. But it is of note that the three patients whose choroidal tubercles changed to what we consider the final or healed stage, without other tubercles in earlier stages, are clinically well after fairly prolonged observation (all more than seven months); and that of the eight cases in which in spite of prolonged treatment (over three months) the tubercles failed to progress beyond the early intermediate stage death occurred in five and in the remaining three the response to treatment has been unsatisfactory and recovery seems to be very unlikely.

The following are records of two of the cases mentioned above. They illustrate the possible value of the changes described.

Case 1.—A girl aged 2 years 9 months was admitted with miliary tuberculosis. Four choroidal tubercles were seen in the early stage. She seemed to respond extremely well to streptomycin, and the x-ray picture of the chest became normal. But at the end of four and a half months' treatment, when the question of stopping the drug arose, the choroidal tubercles had not progressed beyond the early intermediate stage. The drug was therefore continued. Meningitis developed, and she died eight months after treatment had been started.

Case 2.—A boy aged 16 months was admitted with miliary tuberculosis. He seemed to respond very well to streptomycin, and the x-ray picture of the chest became clear; but his solitary choroidal tubercle failed to progress beyond the intermediate stage. Treatment was continued for six months—two months longer than the normal duration of treatment given here—and two months after the treatment was stopped tubercle bacilli were cultured from the gastric washings.

The appearance of a new choroidal tubercle after prolonged streptomycin treatment is naturally of bad prognostic significance. We have seen this happen only once.

Case 3.—A boy aged 15 months was treated with streptomycin on account of miliary tuberculosis with meningitis. One choroidal tubercle was found when he was first examined. In spite of four months' treatment this tubercle never progressed beyond the intermediate stage, and the radiograph of his chest showed only a partial clearing of the lung field. Five months after the treatment had been started a new choroidal tubercle was discovered. His fundi had been repeatedly and carefully examined, and it seems unlikely that this tubercle had been missed previously. The tubercle, furthermore, is in the early non-pigmented stage.

It is clear that a great deal more work is required on this subject, and we hope to give a further report in due course.

Choroidal Tubercles in Other Cases of Tuberculosis

It is generally considered that a tuberculous bacteraemia is a common if not usual sequel of a primary tuberculous infection. It would seem possible that if careful search were made of the fundi of all children with primary tuberculosis an occasional choroidal tubercle would be found.

Randolph and Schmeisser (1915-16) stated that choroidal tubercles could be found, though infrequently, in practically any type of tuberculosis with a primary lesion. Brunthaler (1926) described a boy aged 4 with congenital syphilis and epituberculosis. Multiple choroidal tubercles were found. A year later the boy was in good health, and a few small rounded scars of the choroid were present. Weiss (1877) describes the finding of choroidal tubercles at necropsy in a man in whom no other evidence of tuberculosis could be discovered. Cohnheim (1867) said that choroidal tubercles could occasionally be found in cases of tuberculosis without miliary spread.

We have found choroidal tubercles in four such cases, but in two (thought by the physician and the radiologist to have merely a primary complex) the period of observation has at the time of writing been only a very short one (7 and 19 weeks respectively) and it is too soon to exclude miliary spread.

The two other cases, however, are of special interest, for they have both been observed for nine months and both are clinically and radiologically entirely normal. The following is a summary of these cases.

Case 4.—A girl aged 4 was first seen with a six-months history of pain in the right knee. Her tuberculin test was positive and a diagnosis of tuberculosis of the knee-joint was made. Three weeks after admission she was found to have a solitary choroidal

tubercle in the early stage. A radiograph of the chest showed a very doubtful generalized mottling of the lung field which the radiologist did not think was that of miliary spread. Tubercle bacilli were cultured from the gastric washings. Further radiographs were taken at intervals, and they have now been normal for four months or more and the child is well. She has not been given streptomycin or other specific therapy. The x-ray photographs are not reproduced in this article, because the mottling was so fine that it would certainly not show in a reproduction; the x-ray picture would probably have been passed as normal unless miliary tuberculosis had been particularly suspected. The interesting feature of this case is that we observed all the changes in the choroidal tubercle which we have seen in the streptomycin cases. The tubercle is now a parchment-white scar with heavy pigmentation around (Fig. 4).

Case 5.—A boy aged 3 was admitted on account of a tuberculous cervical lymph node. He had a history of recurrent cervical abscesses for two years. His tuberculin test was positive. A radiograph of his chest showed a picture identical with that of Case 3, and for the same reason the radiograph is not reproduced here. Tubercle bacilli were cultured from the gastric washings. A month after admission we found what we consider to be the final or healed stage of a choroidal tubercle (Fig. 6). The child is now perfectly well, and a radiograph of his chest has been clear for over four months. His choroidal tubercle remains unchanged. He too has had no specific treatment.

It is quite possible that both these cases are in fact examples of chronic miliary tuberculosis undergoing spontaneous cure, but in neither case was it possible to make that diagnosis from the radiograph of the chest.

Summary

Choroidal tubercles were found in 7 out of 14 cases of miliary tuberculosis without meningitis, and in 18 out of 28 cases of miliary tuberculosis with meningitis. In other words, they were found in 25 (60%) out of 42 of all the cases of miliary tuberculosis. They are therefore of great diagnostic value in these cases. They may establish a definite diagnosis before a radiograph of the chest or a lumbar puncture has been performed.

Choroidal tubercles were found in only one out of 18 cases of tuberculous meningitis without miliary spread.

In nine of our cases necropsy revealed miliary tubercles which had not been detected by x-ray photographs of the chest. It is emphasized, therefore, that in a case of tuberculous meningitis miliary spread can be excluded only at necropsy.

In no cases were choroidal tubercles found merely as a terminal phenomenon. They were found at the time of the first or second examination.

The natural history of the choroidal tubercle is described. As time passes, the margin of the tubercle becomes more definite, the tubercle enlarges, the centre becomes paler, and the tubercle and the surrounding area become stippled with pigment. In the final stage there is a parchment-white scar with heavy surrounding pigmentation and paling of the near-by choroid.

It is suggested that further observation may well show that the changes described are of prognostic value. Of those cases (eight in number) in which in spite of prolonged streptomycin treatment the tubercles failed to progress beyond the early intermediate stage, death has occurred in five and the remaining three are doing badly. All the cases in which the tubercle progressed to the parchment-white appearance without any tubercles in earlier stages were apparently cured.

Choroidal tubercles were found in four cases of tuberculosis in children in which there was no meningitis or certain evidence of miliary spread. In one of these cases a solitary choroidal tubercle was seen to pass through all the stages described above to the final or healed stage. It seems possible that careful examination of the fundi of all cases of primary tuberculosis will, in some, reveal choroidal tubercles.

Our thanks are due to Professor E. J. Wayne and Professor C. H. Stuart-Harris for allowing us to see their cases; to Drs. J. Burke, M. Powell, and J. Briggs for helping in the examination of fundi; to Mr. B. Nutt, ophthalmic surgeon, for advice; to Dr. J. L. Emery for the histology; and to Dr. T. Colver for letting us see his cases. The paintings are by Messrs. Hamblin.

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LEGENDS

FIG. 1.—Choroidal tubercle, early stage, on commencement of streptomycin treatment.

FIG. 2.—Very early choroidal tubercle at 3 o'clock. Several others in slightly later stages. Choroidal tubercles at intermediate stage at 7 and 11 o'clock. (After six weeks' streptomycin treatment.)

FIG. 3.—Late stage of choroidal tubercle at 3 o'clock, with two other tubercles in early intermediate stage. Case of miliary tuberculosis with meningitis which failed to respond to streptomycin.

FIG. 4.—"Healed" choroidal tubercle, Case 4, at end of six months' observation. Case of tuberculosis of knee without evidence of miliary infection. No specific treatment.

FIG. 5.—"Healed" choroidal tubercle. Case of miliary tuberculosis with meningitis on completion of streptomycin treatment, apparently cured.

FIG. 6.—Healed choroidal tubercle (Case 5). Case of primary tuberculosis without evidence of miliary spread or meningitis. No specific treatment.

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