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SOME PROBLEMS IN THE DIAGNOSIS OF MENINGEAL TUBERCULOSIS

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IT is, I think, becoming increasingly clear that the fatality rate in tuberculous meningitis treated with streptomycin bears no small relationship to the stage of disease at which treatment is instituted. The importance of early diagnosis has made us conscious of the many difficulties associated therewith, and in particular much attention has had to be focused on lymphocytic exudates (and sometimes polynuclear too) in the cerebro-spinal fluid. In King's Cross Hospital, Dundee, where a streptomycin treatment centre has been in operation for about eighteen months, we are fortunate in having thirty beds available for the observation and treatment of children suffering from either pulmonary or non-pulmonary tuberculosis. Most of the pulmonary cases are discovered by routine examination of contacts, and with a comparatively small waiting list the period between diagnosis and admission to hospital is not lengthy.

The children are nursed in a bright well-ventilated ward with adequate balcony facilities. They are kept in bed—I would hesitate to say at rest, for that is impossible when dealing with this type of patient who is, most often, an extremely lively and to all outward appearances a normal child. They are given a good mixed diet and their appetites are usually, to put it mildly, unimpaired. Temperature, pulse and respiration rates are recorded twice daily and serial X-rays are taken at intervals of one to two months. I draw this picture because it is of considerable importance in establishing a base-line of primary tuberculosis which may later be altered by the occurrence of meningitis. Thus it is possible to assess the "normal" in each patient admitted and at the least sign of departure from this immediate steps are taken to ascertain the reason. It is becoming very evident that thecal puncture is one of the first essentials. In little more than a year, an abnormal cerebro-spinal fluid was found in no fewer than 8 of 57 children under observation, and it is with the consideration of these that this paper is mainly concerned.

Read at a meeting of the Tuberculosis Society of Scotland held at Dundee on 1st April 1949.

Case Records

Case No. 1.—(J. McL.), a female child, aged $1\frac{9}{12}$ years, was admitted on 28th January 1948 with a family history of tuberculosis, a positive Mantoux and radiological evidence of right hilar adenitis with the later development of opacity of the entire upper lobe of the right lung. In spite of this she remained quite well until 7th March when she was sick and listless, had loose stools and a rise of temperature. She was better over the next few days, but on 11th March sickness recurred and she became irritable. Lumbar puncture gave the following results: fluid under increased pressure; cells 200/c.mm. mainly lymphocytes; protein 50 mgms. per cent.; Lange 5555444322. Fluid was injected into a guinea-pig, which, killed at 8 weeks, was found healthy, and two cultures were also negative for B. tuberculosis. These were, of course, retrospective findings, and treatment with streptomycin had begun on 11th March (*i.e.* 5th day of symptoms). Response to therapy was good, the temperature subsiding in a week and the clinical condition returning to normal. Treatment was stopped after 16 weeks. Serial cell counts over the next 7 months showed a gradual return to normal (200, 185, 270, 110, 37, 20, 14, 17, 64, 10, 12, 10, 3). Two post-treatment samples of C.S.F. were cultured and also inoculated into guinea-pigs with negative results. At the beginning of October 1948 (*i.e.* a full 7 months after the initial onset of meningitis) there was a relapse with clinical signs of meningitis and an abnormal C.S.F. This time three cultures of C.S.F. were all positive for B. tuberculosis (human type) and two inoculated guinea-pigs were both found suffering from tuberculosis. The relapse failed to respond to streptomycin and the patient died on 15th November.

Post-mortem examination showed:—

(1) Tuberculous meningitis.
(2) Tuberculoma in wall of lateral ventricle.
(3) Primary lung focus.
(4) Caseating hilar gland.

Case No. 2.—(R. D.), a male child, aged $1\frac{9}{12}$ years, was admitted to hospital on 7th October 1947 with a history of tuberculous cervical glands and radiological appearances of a miliary lesion in the lungs. On admission, Mantoux test was positive, gastric lavage negative and there was radiological evidence of right hilar enlargement only. He was quite well until 21st March 1948, when he became pyrexial and over the next few days developed malaise, headache, anorexia and lethargy. Lumbar puncture on 25th March (*i.e.* 5th day) gave the following results: pressure increased, cells 320/c.mm., mainly lymphocytes; protein 90-100 mgms. per cent.; sugar present. Two cultures of C.S.F. were negative for tubercle bacilli, but an inoculated guinea-pig was found to be suffering from tuberculosis (minimal lesion). Treatment with streptomycin had been begun with apparently good effect, although after 4 months the cell count in the C.S.F. was still 128/c.mm. and a post-treatment sample inoculated into a guinea-pig gave a positive result. On 31st July (*i.e.* a little more than four months after the initial meningitis), there was a relapse. The cultures failed to produce an organism, but once again an inoculated guinea-pig developed tuberculosis. Streptomycin therapy was re-started with good effect and the child is at present well. The latest cell count is 20/c.mm. and a sample submitted for "test of cure" has been reported negative.

CASE No. 3.—(C. B.), a male child, aged $\frac{8}{12}$ year, was admitted on 12th March 1948 with a definite family history of tuberculosis, Mantoux positive, gastric lavage positive (human type) and radiological evidence of a primary complex in the right lung. The infant remained well for less than three weeks, and on 31st March he appeared listless, had loose stools and became pyrexial. Lumbar puncture on 5th April (*i.e.* 6th day) gave the following results: C.S.F. under increased tension; cells 230/c.mm., mainly lymphocytes; protein 100 mgms. per cent.; sugar absent; Lange 3334445554. B. tuberculosis (human type) was cultured from the fluid and guinea-pig inoculation was positive. In spite of streptomycin therapy his condition deteriorated steadily till death on 15th June (*i.e.* ten weeks after the start of treatment). Permission for post-mortem examination was not granted.

CASE No. 4.—(R. L.), a male child, aged 3 years, was admitted to hospital on 12th March with a history of a primary lung complex $\frac{18}{12}$ year previously, the present reason for admission being tuberculous disease of the spine (L.V. 1 and 2). Mantoux reaction was positive and gastric lavage negative. He was apyrexial and appeared well generally until 15th April when he was actively sick and next day became listless and drowsy, with twitching of the left arm. In the evening he had two convulsions, and lumbar puncture done the same evening (16th April) gave the following results: cells 50/c.mm., mainly lymphocytes; protein 20 mgms. per cent.; sugar present; Lange 10×0. Three cultures failed to reveal an organism and an inoculated guinea-pig, killed at eight weeks, was found healthy. The response to streptomycin therapy was rapid and the cell count gradually returned to normal over two months. Post-treatment samples of C.S.F. failed to show tubercle bacilli. He has now been observed for more than ten months and is clinically well from the meningitic viewpoint and cells in the C.S.F. are less than 1/c.mm.

CASE No. 5.—(M. McD.), a female child, aged 4 years, was admitted on 30th April 1948, with a family history of tuberculosis, positive Mantoux reaction and radiological evidence of a primary complex in the lower zone of the right lung. Apart from slight loss of weight she was quite well until 12th June when the temperature rose sharply and clinical appearances suggested acute appendicitis. The condition, however, subsided over the next 48 hours, but she again became pyrexial and was listless. Lumbar puncture was done on 17th June (*i.e.* 5th day) with the following results: pressure increased; cells 340/c.mm., mainly lymphocytes; sugar absent; protein less than 10 mgms. per cent.; Lange 1122220000. Three cultures of C.S.F. were negative for B. tuberculosis, and an inoculated guinea-pig, killed at eight weeks, was healthy. Treatment with streptomycin had been begun. After one week the child was apyrexial and apparently "normal" again. The pleocytosis gradually subsided and the C.S.F. was normal in twelve weeks. A post-treatment sample of fluid was cultured and inoculated into a guinea-pig with negative results. X-ray examination at the end of December showed the primary complex apparently healed and she was discharged from hospital on 24th January 1949. She has remained well to date (*i.e.* about nine months from the onset of meningitis).

CASE No. 6.—(S. E.), a male child, aged $1\frac{1}{2}$ years, was admitted to hospital on 22nd July 1948 with Mantoux positive, gastric lavage negative and radiological evidence of a primary complex in the midzone of the right lung. He

remained well and apyrexial for just over three weeks but on 15th August he was very sick, listless and pyrexial. Lumbar puncture was performed next day (16th August) with the following result: pressure increased; cells 124/c.mm., mainly lymphocytes; sugar present. Two cultures failed to reveal tubercle bacilli and an inoculated guinea-pig, killed at eight weeks, was found healthy. There was a good response to streptomycin therapy, and the C.S.F. was normal cytologically after two months. Treatment was discontinued after 16 weeks and on 7th January 1949 a specimen of C.S.F. was submitted to the bacteriologist for "test of cure." In spite of the fact that the C.S.F. was chemically and cytologically normal, B. tuberculosis was cultured from this sample. The child has now been under observation for seven months and has remained well. A further sample of fluid has been cultured and inoculated into a guinea-pig with negative results.

Case No. 7.—(J. C.), a female child, aged 11 years, was admitted on 28th June 1948 with tuberculous disease of the cervical spine (Mantoux positive, gastric lavage negative, X-ray chest normal). She was apyrexial and quite well generally till the end of August when she complained of recurrent headache. She was apyrexial and there were no signs of meningeal irritation, but lumbar puncture on 2nd September gave the following results: pressure normal; cells 145/c.mm., mainly lymphocytes; sugar normal; protein 50 mgms. per cent.; Lange 10×0. Two cultures of C.S.F. were later reported negative for B. tuberculosis and an inoculated guinea-pig killed at eight weeks was healthy. Meanwhile streptomycin therapy had been begun on 2nd September. The clinical condition quickly returned to normal (it was never far removed), and when treatment was discontinued after sixteen weeks she was apparently well. She had been off treatment for only ten days when she began to have infrequent bouts of sickness and headache. On 10th January 1949 treatment was restarted but she continued to have bouts of headache and sickness, being apparently normal in the intervals. On 10th February she had double vision and there was paralysis of both 6th nerves. She died quite suddenly on 12th February. Cultures and guinea-pig inoculation of the C.S.F. were negative, but post-mortem examination confirmed the diagnosis. A summary of the findings was as follows:—

(1) Caseous mesenteric gland.
(2) Healed scar upper right lung.
(3) Caries 2nd and 3rd cervical vetebræ.
(4) Gross dilation of lateral ventricles with tuberculoma in wall of the right ventricle. Thin basal film of exudate (both 6th nerve nuclei involved).

Summarising the findings, therefore, lymphocytic exudates, with relatively minimal clinical signs, developed in seven children under observation for known tuberculous lesions. The essential features are summarised in Table I. It will be seen that the most constant clinical features were listlessness, pyrexia and sickness in that order. In only two cases (Nos. 2 and 3) was the diagnosis of tuberculous meningitis confirmed at the onset by recovery of the organism. A further three were confirmed at later dates (Table II) and the position to date is that only two remain unconfirmed bacteriologically.

The lack of bacteriological confirmation led us to consider the nature of the occurrence of many of these lymphocytic exudates. In order to establish a base-line it was decided to perform thecal puncture

TABLE I

Clinical Details in 7 Patients with a Known Tuberculous Lesion who Developed Lymphocytic Exudate in C.S.F.

Case.	Site of Initial Lesion.	Symptoms—Meningeal Involvement.		C.S.F. at Initial Thecal Puncture.							
		Symptoms.	Duration (Days) before L.P.	Appear.	Pressure.	Cells/c.mm.	Sugar.	Protein.	Lange.	Culture.	G.-Pig.
1. (J. McL.)	Lung	Listlessness, pyrexia, sickness, diarrhœa	4	Cl.	+	200	+	50	Early	—	—
2. (R. D.)	Lung	Lethargy, pyrexia, headache, anorexia	5	Cl.	+	320	+	90	...	—	+
3. (C. B.)	Lung	Listlessness, pyrexia, diarrhœa	5	Cl.	+	230	—	100	Late	+	+
4. (R. L.)	Lung Spine	Listlessness, sickness, twitching, anorexia	2	Cl.	N.	50	+	20	N.	—	—
5. (M. McD.)	Lung	Lethargy, pyrexia, abdominal pain	5	Cl.	+	340	—	10	Mid.	—	—
6. (S. E.)	Lung	Listlessness, pyrexia, sickness	2	Cl.	+	124	+	...	...	—	—
7. (J. C.)	Spine	Headache	3	Cl.	N.	145	+	50	N.	—	—

in a group of children with a primary lung complex but who were otherwise normal (*i.e.* apyrexial and well generally). This was done in sixteen children, in each of whom the C.S.F. was found to be normal,

TABLE II

Showing Results of Attempts to Confirm Infection of Meninges with B. Tuberculosis

Case.	Organism Isolated.				Organism not Isolated.
	Onset.	"Test of Cure."	Relapse.	Post-mortem.	
2. (R. D.) . .	+	...	+	...	...
3. (C. B.) . .	+	...	...	...	...
6. (S. E.) . .	...	+	...	...	...
1. (J. McL.) .	...	...	+	...	...
7. (J. C.) . .	...	...	...	+	...
4. (R. L.) . .	...	...	...	...	+
5. (M. McD.) .	...	...	...	...	+

chemically and cytologically. In a further group of six children, all with a primary tuberculous lesion but who had been "out of sorts," the C.S.F. again showed no apparent abnormality. Bacteriological examination was not carried out in either group.

CASE No. 8.—(W. C.), a male child, aged 4½ years, was admitted to the tuberculosis unit on 18th June 1948, having been transferred there from another ward in the hospital following an attack of whooping cough complicated with pneumonia. The Mantoux test was positive and there was radiological evidence of a primary tuberculous lesion in the lower zone of the left lung. There was no family history of tuberculosis. On 24th August 1948, lumbar puncture was done for experimental purposes referred to above, and the fluid was normal. On 27th August he was very sick and there were definite clinical signs of meningeal irritation. Lumbar puncture (27th August) gave the following results : pressure normal ; cells 150/c.mm. (lymphocytes) ; protein 50 mgms. per cent. ; sugar present ; Lange reaction 10×0.

As he was not particularly drowsy, and bearing in mind previous experience, streptomycin therapy was withheld temporarily. Within 48 hours signs and symptoms had disappeared and the cerebro-spinal fluid returned to normal in 14 days. A culture of the initial abnormal C.S.F. was unfortunately contaminated, but an inoculated guinea-pig, killed at eight weeks, was found healthy. The child remains well to date, approximately seven months after the occurrence of meningeal involvement.

DISCUSSION

Several general conclusions may be made from the study of this small investigation. Firstly, primary tuberculosis, *per se*, does not appear to cause any abnormality, chemical or cytological, in the cerebro-spinal fluid. I have no evidence as to whether organisms may or may not be present. Secondly, minor upsets in children suffering from primary tuberculosis may or may not be associated with an abnormal C.S.F. Lastly if a lymphocytic exudate *is* present it may or may not be possible to demonstrate tubercle bacilli in the fluid.

It is in the proper interpretation of a lymphocytic exudate occurring in a child known to be suffering from tuberculosis that difficulty has been encountered. The causes of lymphocytic exudate in C.S.F. are many and cover the fields of primary viral infections, secondary post-infective meningo-encephalitis and a miscellaneous group of infections due to bacteria, spirochætes, yeasts, etc. While investigation for virus agents was not done, it seems reasonable to assume that in a child hospitalised with a primary tuberculous lesion the occurrence of a lymphocytic exudate in the C.S.F. is most likely to be associated with the tuberculous infection, either because of a true tuberculous meningitis or a serous meningitis of tuberculous ætiology.

Rich and McCordock in 1933 questioned the original view that tuberculous meningitis was due to a direct hæmatogenous infection of the meninges. They found focal caseous lesions, in communication with the meninges, older than the meningitis in 77 out of 82 brains studied. McGregor and Green confirmed these findings in 74 out of 88 cases examined. While several writers have not agreed with this concept, there is, I think, a growing belief that it is the correct one and that tuberculous meningitis is secondary to a focus in the choroid plexus or a focus in the brain itself, communicating with the ventricular

system or the subarachnoid space. If this view is accepted then it makes it easier to understand the possible pathogenesis of serous meningitis of a tuberculous nature, which may well be due, as suggested by Lincoln, to a perifocal reaction around a tuberculous focus already established in the brain. Furthermore, such a pathology would appear to fit the variations in the clinical picture of serous meningitis which have been reported.

MacGregor and others (1934) described three patients with primary tuberculosis who developed meningeal signs and in whom tubercle bacilli were recovered from the C.S.F., the fluid being abnormal cytologically and chemically in only one. Choremis and Vrachnos (1948) described two patients in whom tubercle bacilli were isolated by culture from the C.S.F., the fluid being virtually normal chemically and cytologically (one patient had 8 cells/c.mm. and chloride was said to be 540 mgms. per cent.). This picture of organisms without cellular reaction contrasts with the opposite picture of cells without organisms described by Lincoln (1947). She described twelve cases of serous tuberculous meningitis. In eight of these the diagnosis was apparently made on clinical evidence of meningeal irritation alone, there being no changes cytologically, chemically or bacteriologically. In the remaining four, lymphocytic pleocytosis was present without chemical or bacteriological changes. Rubie and Mohun (1949) have recently reported five patients showing evidence of tuberculous infection who developed "meningism" with an abnormal C.S.F., who were not treated with streptomycin and who all recovered, the C.S.F. reverting to normal in periods varying between 2 and 23 days. There is no indication in the paper as to whether B. tuberculosis was or was not present in the fluid.

The findings in my own series of cases are complicated by the fact that all but one were treated with streptomycin on the evidence of a lymphocytic exudate in the C.S.F. in the presence of a known primary tuberculous lesion. It seems more than possible that several of these patients might well have recovered, initially at least, *without* streptomycin. One case (No. 3) was obviously suffering from tuberculous meningitis from the start. In the two patients (Nos. 1 and 7) who died following a relapse, post-mortem examination showed in each a tuberculoma in the wall of the lateral ventricle, and their initial symptoms could presumably have been due to a perifocal reaction. MacGregor and others (1934) refer to the work of Cramer and Bickel who collected 46 cases of recovery from tuberculous meningitis, confirmed by demonstration of the organism, and who stated that "in many of these recovery was temporary and death followed within a few months from recurrence of meningitis or from the effects of tuberculosis elsewhere." The remaining five patients in my series (four treated, one untreated) are all well to date. Of these, two are confirmed and three unconfirmed bacteriologically. The untreated case was presumably suffering from serous meningitis, and I believe

that at least three of the treated cases (Nos. 4, 5 and 6) may have been due to the same condition.

Lincoln attempted to differentiate between serous meningitis and tuberculous meningitis. Nothing she has written has altered my opinion that the two simply cannot be differentiated in their early stages, and that it is only the progressive nature of tuberculous meningitis that can ultimately decide.

What then is the policy to be when dealing with an abnormal C.S.F. in a child with a known tuberculous lesion? We know that the progress of tuberculous meningitis in the young child can be extremely rapid. I have recently seen a child who was irritable one day, developed a focal nerve palsy the next, was comatose the next and who failed utterly to respond to streptomycin therapy, started at the stage of the nerve palsy. Nevertheless I believe that in the majority of cases one can, at least for a day or two, watch developments in doubtful cases. Meningism, local muscular twitchings and even convulsions can occur in both conditions, while in the early stages the findings in the C.S.F. may run parallel. The factors which I believe to be of importance in indicating tuberculous meningitis are, in order of importance, increasing drowsiness and reduction of the sugar content of the C.S.F. If one or both of these factors are present, then streptomycin therapy should be begun without delay and confirmation, or otherwise, of the diagnosis awaited from the result of cultures and guinea-pig inoculation of the cerebro-spinal fluid.

Conclusions

Since the introduction of streptomycin has altered the prognosis in tuberculous meningitis, it is now of the utmost importance that abnormality of the cerebro-spinal fluid should be recognised as early as possible in children with a primary tuberculous lesion, even although such abnormality can be explained on the basis of a benign serous reaction. It would seem that such a benign reaction may disappear without treatment and the cerebro-spinal fluid remain normal, in which case one may be justified in the presumption that the causal intracerebral lesion has healed, but obviously longer periods of observation of individual cases will be necessary before one can be certain. On the other hand, if a child has had a benign serous reaction he would require careful watching since, presumably, a true tuberculous meningitis could supervene at any time as a result of progression of the intracerebral focus. Since abnormality of the cerebro-spinal fluid can be present with minimal clinical signs, it is suggested that thecal puncture, while never to be undertaken lightly, should nevertheless be seriously considered as an early step in all cases in which there is the slightest deviation from the clinical "normal" in a child with a primary tuberculous lesion.

Addendum

Recently a further case has arisen in a male child aged 4 years. This child was in hospital with a tuberculous lesion of the upper left lung (Mantoux reaction positive, gastric lavage negative) and had been under observation for about eleven months, his general condition being good and his temperature normal. On 2nd April 1949 the temperature was elevated and next day he was complaining of headache, and was flushed, irritable and drowsy. Lumbar puncture gave the following results : fluid under markedly increased pressure ; cells 6/c.mm. ; sugar normal ; protein 40 mgms. per cent. ; Lange 2333444555. On 4th April the cells were 10/c.mm., and on 5th April were 20/c.mm. By 9th April the clinical condition had returned to normal and the C.S.F. was normal by 15th April, without streptomycin therapy. Results of cultures and guinea-pig inoculation of C.S.F. are awaited with interest.

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