Study in the Therapy of Transverse Myelitis Occurring During Tuberculous Meningitis

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Transverse myelitis appearing during the course of tuberculous meningitis is one of the main reasons for its poor prognosis. Fortunately, this condition is relatively infrequent and, it is possible with prompt and appropriate therapy it can be significantly reduced.

Spreading of the infection in the medulla spinalis is mainly due to contamination of the meninges during tuberculous meningitis. Localization of Mycobacterium tuberculosis in the medullar substance through the circulation in generalized tuberculosis is uncommon.

In the international literature, only a few cases of tuberculous meningomyelitis are reported. Kupka and his collaborator, Harbitz, Kreschner and his collaborator, and Rigton, have presented a number of cases.

Fischer reported 20 cases of myelitis in the course of tuberculous spondylitis caused by compression of vertebrae and cold abscess formation.

At Sotiria Sanatorium, in our clinic, we treated 209 cases of tuberculous meningitis and observed only six cases of transverse myelitis, which appeared in the course of tuberculous meningitis insufficiently treated at places other than our institution. Three of them died, and necropsies were performed.*

Report of Cases

We consider essential the detailed presentation of cases in order to render our conclusions clearer.

Case 1: D. M., a man clerk, aged 27, was found to have pulmonary tuberculosis in August 1952. Biochemical treatment for eight months was insufficient. In 1952, he had tuberculous meningitis and for 55 days he was treated insufficiently in his house. Treatment there consisted of intraspinal injections of streptomycin combined with small doses of INH. In March 1953, he was transferred to our clinic. He had a high fever, diminsh of mental functions, spasms with hyperexcitability and all the clinical symptoms of meningitis. Laboratory examination of cerebrospinal fluid showed 650 cells per cc., 56 per cent being lymphocytes and 2.5 gr./100 cc. of protein and Mycobacterium tuberculosis.

Other findings were rectovesical disturbances, spastic paresis of the lower extremities with heightened tendon reflexes, disturbance of sensitivity and extensive necrotic changes of the gluteal and sacrombar skin regions. Thus, it was a meningomyelitis case.

Intraspinol streptomycin was discontinued and followed by persistent antituberculous drug therapy. Improvement of meningitis was marked. The cerebrospinal cell count fluid and protein decreased. The medullar symptoms, however, were accentuated, the spastic paresis turned flaccid, the retentions of urine and feces increased, as well as the skin necroses. The patient's condition progressively became worse and four months later he died.

On post-mortem examination the brain was edematosus, the cerebral ventricles dilated and filled with turbid cerebrospinal fluid; in the base of the brain a considerable amount of viscous and glutinous exudate was found; the spinal meninges were much thickened and in places, small pockets of fluid adhered; in the thoracic region of the spinal column, a good sized pocket of fluid was found where the pia mater firmly

*The histology examinations were made by Professor D. Eleftheriou to whom we extend our thanks.

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adhered to the spinal cord. Transverse dissection at this very point showed complete transverse degeneration with necroses, and it was impossible to distinguish between the white and grey matter. Histological study revealed, in addition to necrotic and degenerative substances which occupied all the transverse segment of the cord, peripheral necrosis like a geographical map. In the destructive changes of medullar substance, scattered tubercles were found. The walls of the vessels of the subarachnoid cavity were infiltrated and many of them were completely plugged. The vessels of the spinal meninges showed periadvential infiltrations with many tubercles.

We concluded that it was a case of diffuse transverse myelitis involving the thoracic region of the spinal cord, caused by tubercle localization in the medullar substance from contiguous tissues. In this case, the accentuation of the disease and the diffuse destruction of the transverse medullar segment was due to the progressive compression of the spinal cord by the encysted pocket of fluid. This pocket formation was due to the adherent meninges.

Case 2: S. D. This man, a laborer aged 32, reported having pulmonary tuberculosis in March 1952. In March 1953, he had tuberculous meningitis and was hospitalized. For three months, the treatment consisted of intraspinal injections of streptomycin and small doses of INH. In June 1953, he was transferred to our clinic, where he had fever, opisthotonos, and total mental dinniness. Cerebrospinal fluid examination showed 770 cells per cc. and 16 gr./100 cc. of protein. Spastic paresis of the lower extremities, positive Babinski’s sign, foot clonus, exaggerated reflexes, and hyperesthesia were also present. Other findings were rectovesical disturbances, e.g., alternate retention and loss of rectal and vesical control.

Although the intraspinal injections of streptomycin were discontinued and large doses of INH and PAS were intravenously administered, he became worse. A month and a half later, spastic paresis turned flaccid, extensive nutritional disorders of the skin appeared, and loss of rectal and vesical control occurred. His condition gradually became worse, and in the fourth month following hospitalization he died.

Post-mortem findings revealed marked increase of cerebrospinal fluid with edematous encephalic substance. The spinal meninges were thickened and at places adherent to themselves and the medulla spinalis. In certain points between the meninges small pockets of turbid fluid were found; dissection at the adherent points of the medullar substance and the pia mater showed degenerative changes and necroses of the whole transverse segment; the histological findings showed degenerative necrotic destruction of the medullar substance with small, sparse tubercles; infiltrations and thromboses of the vessels of the subarachnoid cavity and extensive degenerative changes of the spinal meninges were also found. We concluded that this was a case of diffuse transverse myelitis with multiple foci in the medullar substance.

Case 3: I. D., male. This farmer, aged 45, had pulmonary tuberculosis five years ago. In April 1953, he had tuberculous meningitis and entered a hospital. Treatment consisted of intraspinal injections of streptomycin, PAS, and INH. The second month following the intraspinal injection therapy, although he showed slight clinical improvement, medullar phenomena appeared. He was admitted to our clinic. His condition was grave. Besides meningitis symptoms and the findings in the cerebrospinal fluid, he also had flaccid paralysis of the lower extremities, loss of rectal and vesical control, and extensive skin necroses.

Intraspinal injections were discontinued and usual chemotherapy followed. His condition, however, progressively became worse and in two months, that is five months following the infection, he died. Microscopic study revealed multiple diffuse transverse spinal destruction in different levels. Small tubercles in the medullar substance were also seen. Extensive adherent processes of the spinal meninges, accompanied by periadvential infiltrations and a plugging of the vessels, were also seen. We concluded that it was a tuberculous meningomyelitis case with multiple medullar foci.

Case 4: P. E. This laborer aged 21 had acute miliary tuberculosis in March 1952. Two years later, tuberculous meningitis was present. He was treated insufficiently with intraspinal injections of streptomycin, PAS, and INH. After two months of therapy, he also had symptoms of meningomyelitis.

He was transferred to our clinic with meningitis symptoms; abundant cerebrospinal fluid findings, spastic paresis of the lower extremities, exaggerated reflexes, positive Babinski’s sign, foot clonus, nutritional skin disorders and rectovesical disorders.

Intraspinal injections were immediately discontinued and usual chemotherapy was initiated, supplemented by 12 mgs. per Kg. body weight of Sulfone J.S1, daily.

Ten days later his condition improved considerably and within 45 days, all meningitis symptoms had disappeared. Medullar symptoms were also improving. Four and a half months later, almost all spinal symptoms had disappeared to the point that he could move freely. A slight spastic gait was the sole effect of the disease, which with electrotherapy and massage was improved to the extent that he was discharged as clinically cured. A year later, he was in excellent condition, exhibiting only a slight spastic gait.
We conclude in this case that the J.51 addition in meningomyelitis treatment contributed to the cure of the disease, leaving few residuals.

Case 5: S. I. This man a clerk aged 26, was hospitalized for tuberculous meningitis in February 1952. He was treated insufficiently with intraspinal injections of streptomycin and INH. In May 1954, he had a new paroxysm of meningitis and was brought to our clinic. He also had transverse myelitis symptoms affecting the lumbar region of the spinal cord. The cessation of intraspinal injections was followed by intravenous administration of INH, PAS, and sulfone J.51, 14 mg. per Kg. body weight. After four months of treatment the meningitis symptoms disappeared altogether, the cerebrospinal fluid was normal, and the myelitis symptoms showed improvement. The rectovesical and nutritional disorders of the skin disappeared. Sensitivity became normal, and the spastic paresis of the extremities improved.

Eight months after this therapy was started, he was clinically cured except for a slight spastic walk, which was treated with electrotherapy, massage, and vitamin B, besides the other medication. He was dismissed in excellent condition.

Case 6: G. L. This man a student aged 22, had exudative pleurisy in March 1955. Eight months later, he was treated for tuberculous meningitis in a State hospital. The three-month treatment consisted of intraspinal injections of streptomycin and small amounts of PAS and INH without evident improvement. Moreover, he had rectovesical disorders and spastic paresis of the extremities. When admitted to our clinic he had chronic tuberculous meningitis and transverse myelitis. Discontinuation of intraspinal injections was followed by large doses of INH, PAS, and sulfone J.51 in doses of 14 mg. per Kg. body weight. This treatment was continued for six months. The meningitis symptoms disappeared, the cerebrospinal fluid became normal and urine and feces retention as well as skin abnormalities disappeared. The spastic paresis of the extremities improved. After eight months, he was dismissed as chronically cured with only a slight spastic walk residual.

Comment

Myelitis, depending on the total or partial damage of the transverse segment of the cord, is distinguished as diffuse or disseminated respectively. According to its duration, it is designated as acute, subacute, or chronic. Symptomatology depends upon type and extent of damage to the medullar substance. In acute myelitis symptoms appear at once and consist of total disappearance of mobility, anesthesia, as well as loss of reflexes caudal to the damage, consequent of which is flaccid paralysis of the lower extremities, vesica urinaria, and rectum, and extensive nutritional disturbances of the skin in the form of necroses also appear. On the other hand, the symptomatology of subacute or chronic myelitis is different and appears gradually. The reflexes do not disappear, muscle tone remains, rectovesical disorders alternately improve or grow worse. The nutritional disturbances of the integument appear gradually and are localized, Babinski's sign and foot conus appear early, and areas inferior to the damage have normal sensation.

The first three of our cases were diffuse transverse myelitis, as destruction involved the whole segment of the cord. In the last three subacute disseminated cases, the lesions, because of the intense therapeutic administration and especially because of the addition of sulfone J.51, not only did not extend but were even inhibited and gradually healed, leaving slight after effects in the motor region of the cord.

Through detailed tests of the reaction and sensitivity of the skin from the inferior towards the superior layer, we found that in the first case of transverse myelitis the thoracic region of the column was affected. In the second and third cases the myelitis was located in the thoracolumbar and sacral regions respectively. Morbid anatomy verified our findings.

In the remaining three cases, we proved clinically that the damage was
in the lumbar region and that the destruction was disseminated. Necropsy
also revealed that the destruction in the first three cases was diffuse.
In the first case, in addition to necrotic and degenerative changes of the
white and grey substance, sparse tubercles were also found. The walls
of the vessels of the subarachnoid cavity were infiltrated and plugged.
At the points where there were destructive changes in the medulla the pia
mater was firmly adherent to the medulla spinalis. Between the two
meninges there was a pocket of turbid fluid, the walls being the adhesions
of the two meninges.

From the above, one may conclude that the infection of the medullar
substance was caused by direct extension, and the peripheral necroses
were due to a plugging of the vessels. The total damage of the trans-
verse segment was caused not only because of the tuberculous localiza-
tion but mainly from the gradual compression of the medullar segment
by the encysted pocket of fluid.

In the second and third cases, besides total transverse destruction in
different levels of the cord, we also found a complete adherent process
of the meninges, as well as multiple tiny pockets of turbid cerebrospinal
fluid, in the whole of the vertebral canal.

It is known that such localized or extended medullar necroses are
also caused by cancer, syphilis, and arteriosclerosis. The differential
diagnosis, however, is based on laboratory, clinical and x-ray findings.

In the remaining three cases, the cessation of intraspinal injections
was followed by persistent biochemical therapy with large intravenous
doses of INH and PAS and, in addition, doses of 12-14 mg. per Kg. body
weight of sulfone J.51. As a result, the subacute disseminated transverse
myelitis showed no tendency to grow worse, but on the contrary the symp-
toms gradually disappeared and the patients were finally discharged as
clinically cured with only slight effects from the motor region of the
spinal cord. For over a year, the patients are seen regularly and their
condition is excellent.

In all our cases of tuberculous meningomyelitis, prolonged therapy
of intraspinal injections of streptomycin had preceded. We believe that
this point is of considerable importance.

As was reported in a previous study that streptomycin injected in-
traspinaly causes intensive stimulation of the meninges. This is proved
by the fact that following intraspinal injections a considerable increase
of cells in the spinal fluid is noted, accompanied by paroxysms with men-
ingeal symptoms. In certain cases during intraspinal administration of
streptomycin and during the period of improvement, we observed that
the disease grew worse. We interpreted this as recurrence. However,
the paroxysms disappeared as soon as the intraspinal injections of strep-
tomycin were discontinued. The intensive stimulation of the meninges
by streptomycin and the daily injury from the needle contributed to the
formation of adherent processes and their disagreeable consequences.
In all of the dissected cases in which intraspinal injections had been
given, extensive adhesions of the meninges with encysted pocket forma-
tions filled with cerebrospinal fluid with corresponding medullary destruction was a constant finding. The paroxysm of the meninges, inflammation, and the adhesion process contribute to the expansion of contamination in the medullary substance and the destruction of the vessels of the subarachnoid cavity, resulting in deficient blood supply to the medullar substance and consequently a degeneration and necroses of the corresponding medullar segments.

Having this in mind, we have for some years omitted intraspinal injections of streptomycin, and since then, have never observed a case of meningomyelitis.

Special attention should be drawn to the fact that in three out of six cases in which, in addition to antituberculosis drugs, we also administered J.51, we succeeded in preventing further meningomyelitis developments and in bringing about an almost complete cure. We have used J.51 (Sulfone thymole) for three years in our clinic at Sotiria Sanatorium. The results were excellent, especially in the treatment of tuberculous meningitis, since 96.7 per cent of the patients recovered completely. They are still immune after long treatment and by treatment in large dosages. The effectiveness and immunization is confirmed by other authors. Furthermore, the advantage of J.51 is that it retards the occurrence of streptomycin resistance.

We cannot yet give an explanation for the way J.51 acts in the treatment of tuberculous meningitis and myelitis. All our attempts to trace the drug in the cerebrospinal fluid, blood, and urine have failed. A good number of investigators feel that J.51 in vivo breaks up and great amounts of it diffuse in pathologic tissue where it stays for a long time coming in constant contact with the pathologic agent. The foregoing conception, however, does not have a laboratory basis. Undoubtedly, however, J.51 has a valuable therapeutic effect in tuberculous meningitis and myelitis.

CONCLUSIONS

1. In a considerable number of cases of tuberculous meningitis, transverse myelitis may occur and localization of bacilli in the medulla spinalis is primarily due to direct extension.

2. Myelitis appears in cases of prolonged and incomplete therapy of tuberculous meningitis and mainly when intraspinal injections of streptomycin have been administered for a long time.

3. Sulfone J.51 has a considerable therapeutic effect on meningomyelitis, and especially when administered before complete degeneration and necrosis of a spinal segment.

4. Histologic changes of myelitis consist of degenerative and necrotic changes of white and grey matter, accompanied by development of tubercles as well as extensive changes in the subarachnoid cavity vessels.

CONCLUSIONES

1. En un número considerable de casos de meningitis tuberculosa puede ocurrir la mielitis transversa y localización de bacilos en la médula, se debe en primer lugar a retención.
2. La mielitis aparece en casos de terapéutica prolongada e incompleta
   de la meningitis tuberculosa y principalmente cuando se han hecho inye-
   ciones intraspinales de estreptomicina por largo tiempo.
3. La sulfona J.51 tiene un efecto terapéutico considerable en la menin-
   gomielitis y especialmente cuando se administra antes de la degeneración
   y necrosis de un segmento espinal.
4. Los cambios histológicos de la mielitis consisten en degeneración y necrosis de las substancias blanca y gris acompañadas de desarrollo
de tubérculos así como extensos cambios en los vasos del espacio suba-
racnoideo.

RESUME
1. Dans un grand nombre de cas de méningite tuberculeuse, une myé-
lite transverse peut survenir, et la localisation des bacilles dans la moelle
épine est due en premier lieu à la rétention directe.
2. La myélite apparait dans les cas de traitement prolongé et incom-
plet de méningite tuberculeuse, et principalement lorsque injections in-
trarachidiennes de streptomycine ont été administrées pendant longtemps.
3. La sulfone J.51 a un effet thérapeutique considérable sur la méning-
gomyélite, et surtout lorsqu'elle est administrée avant la dégénérescence
complète et la nécrose d'un segment médullaire.
4. Les altérations histologiques de myélite consistent en altérations
dégénératives et nécrotiques de la matière grise et de la matière blanche,
associées à l'apparition de tubercules ainsi que d'altérations extensives
dans des vaisseaux de la cavité sous-arachnoïdienne.

SCHLUSSFOLGERUNGEN
1. In einer beträchtlichen Zahl von Fällen von tuberkulösen Meningitis
kanne eine Querschnitts-Myiélitis auftreten, und die Lokalisation von
Bazillen in der medulla spinalis ist in erster Linie die Folge dirkterRe-
tention.
2. Die Myelitis tritt auf in Fällen von langdauernder und unvollständi-
ger Therapie der tuberkulösen Meningitis und hauptsächlich, Wenn von
intralumbalen Streptomycin-Injektionen lange Zeit hindurch Gebrauch
gemacht wurde.
3. Die Schwefelverbundung J51 übt einen beträchtlichen therapeutischen
Effekt aus auf die Meningomyelitis, besonders bei Anwendung von kom-
pletterer Degeneration und Nekrose eines spinalen Segmentes.
4. Die histologischen Veränderungen der Myelitis bestehen in degenera-
tiven und nekrotischen Veränderungen der weissen und grauen Substanz
in Verbindung sowohl von Tuberkeln als auch ausgedehnten Veränderungen
an den Gefässen des Subarachnoidalraumes.

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