RESUME

Dans le cas rapporté, une radiographie anormale, l'aspect histologique d'une biopsie ganglionnaire, l'augmentation de volume de la rate et des ganglions permirent le diagnostic de sarcoïdose.

Les lésions radiologiques montrèrent une régression marquée pendant les derniers mois de la grossesse, si bien qu'elles avaient virtuellement disparu au moment de l'accouchement. Après l'accouchement, les ombres radiologiques reprirent leur aspect anormal antérieur.

Etant donné le peu de cas publiés, il est indispensable de rassembler beaucoup plus de faits avant de pouvoir déterminer si les modifications enregistrées appartiennent à l'évolution de l'affection ou si elles sont attribuables à quelque altération physiologique de l'organisme pendant la grossesse.

REFERENCES


Report of a Case of Miliary Tuberculosis and Tuberculous Meningitis Treated with Isoniazid

KATHRYN B. SCHWERMA, M.D. and PAUL J. LAWRENCE, M.D.

Madison, Wisconsin

This report is intended to show the effect of prolonged treatment with isoniazid in a case of miliary tuberculosis and tuberculous meningitis. Its presentation at this time, more than two years since isoniazid has become a widely accepted anti-tuberculous drug, seems to us to be justified by the scarcity of reports in the medical literature of this country of its use as the sole chemotherapeutic agent in the treatment of miliary and meningeal tuberculosis, and by the long period of observation following the arrest of active disease in this patient. In 1952 Clark et al1 described their results with a small series of cases which led them to infer that isoniazid was equal or superior to streptomycin in its anti-tuberculous activity. At Municipal Contagious Disease Hospital in Chicago seven of 13 patients with meningitis treated with isoniazid alone survived for six months or more. These results were considered by the authors of this report2 to have been as good as those obtained with isoniazid plus streptomycin. From the journals of foreign countries have come additional evidences of the ef-

Lake View Sanatorium.
fectiveness of isoniazid. A report from England\(^3\) described seven patients with meningitis all alive and well six to twelve months after a sixteen-week course of isoniazid. Similar articles have appeared in France,\(^4\) Portugal,\(^5\) and elsewhere. We now add our observations of a woman treated with isoniazid alone (except for an initial four-week period of streptomycin and para-aminosalicylic acid) and followed for more than two years, through pregnancy and childbirth.

This 19-year-old housewife of Scandinavian descent, was transferred to the county sanatorium from a general hospital on April 5, 1952. Her condition had been diagnosed three weeks before the transfer as miliary tuberculosis. Investigation revealed that her Mantoux test had been negative while she was in grade school and that her photofluorograms had been negative while she was in high school. During the year prior to the clinical onset of the disease she had been working in an office with a person who was later found to have far advanced pulmonary tuberculosis, but there had been no indication of her own ill health until the time that vomiting of pregnancy had its onset in October, 1951. During the next three months vomiting and nausea became moderately severe and she suffered weight loss of approximately 10 pounds. On March 15, 1952, after a two-month period of apparent improvement, she developed fever of 104\(^\circ\). She was hospitalized immediately and rapidly developed severe dyspnea and cyanosis as part of what appeared to be a terminal condition. Examination revealed that the liver and spleen were tender and slightly enlarged. She had a white blood cell count of 2,500,000 cells per cubic mm. and 7 grams of hemoglobin per 100 cm. Oxygen inhalation and blood transfusions were administered. On March 17 her temperature reached 106\(^\circ\); a chest x-ray film then showed miliary pulmonary lesions. She was immediately placed on 2 grams of streptomycin intramuscularly daily (later reduced to 1 gram), and para-aminosalicylic acid, 10 grams orally. The next day she delivered spontaneously a five-month fetus.

When she entered the sanatorium two weeks later (April 5, 1952) she weighed only 90 pounds (20 pounds below her normal weight), had a pronounced pallor, cyanosis of the nail beds, oral temperature of 102\(^\circ\), and slight nuchal rigidity. Lumbar puncture done on April 7 yielded fluid which was positive on culture for tubercle bacilli and contained 16 white cells per cubic mm.

After six days in the sanatorium she suddenly developed a variety of mental and neurological symptoms which indicated tuberculous involvement of the meninges and the cerebral cortex. She was apathetic, unable to communicate, confused, and in poor contact. There was no evidence of disturbed function of the cranial nerves. Motor function was hard to test because of her inability to cooperate and general debility. Reflexes in the upper extremities were hyperactive with ankle clonus more marked on the right side.

Ophthalmological examination revealed small whitish choroidal lesions scattered about both fundi, especially near the discs and maculae. These were conglomerate and were raised slightly. There was no pigment disturbance as yet; the lesions had a fluffy active appearance and the borders were slightly indistinct. Our diagnostic impression was acute chorio-retinitis (OU), with characteristic miliary tubercles.

In spite of the increased mental symptoms, the miliary pulmonary lesions showed x-ray evidence of having begun to clear since the advent of the streptomycin and para-aminosalicylic acid treatment. However, the streptomycin and para-aminosalicylic acid were discontinued on advice (April 15, 1952, after a treatment period of 30 days) and she was placed on a schedule of isoniazid, 100 mg. three times daily. Four days later her temperature dropped from a peak of 102\(^\circ\) to 100\(^\circ\) daily.

Within two weeks she was much more alert, with the sensorium clearer, and contact complete. She exhibited no disorientation, and there was no sign of aphasic disturbances. Reflexes were generally unchanged except that Hoffman's sign was positive and there was no clonus.

By June 6 the choroidal lesions had lost their fluffy active appearance, and although pigmentation remained the same they had subsided noticeably. On June 20 it was observed that the lesions had been reduced still further and that they no longer had an elevated appearance. Several of the small whitish lesions exhibited a fine sprinkling of normal pigment. During this period daily temperature peaks remained at about 100\(^\circ\); spinal fluid findings were normal. (See Table.) Gastric and urine cultures for tubercle bacilli done in April, June, and October were negative. An x-ray film taken on June 25 showed that the miliary pulmonary lesions were clearing rapidly, and by July 15 the lesions had reached their maximum regression. On July 25, examination revealed no further activity in the fundi; and on September 5 the only change was a slightly greater clumping of pigment over a few of the lesions. Since that time no change has been observed in the fundi.
In May, 1953, about 14 months after the clinical onset of miliary tuberculosis, she was discharged from the sanatorium. Since then she has reported as an outpatient for x-ray film and clinical examinations at three-month intervals. In October, 1953, after a normal period of gestation, she gave birth to a healthy infant. When last seen in August, 1955, she presented convincing evidence that her tuberculosis remained inactive. She had been taking isoniazid, 50 mg. three times daily to the present time. That she should have become pregnant within a year of the onset of meningitis, and should now, 22 months postpartum, be in an excellent state of health seem especially significant in view of the long and widely held belief that childbirth exerts a deleterious effect on tuberculosis and in view of the fact that it was during pregnancy that generalized, near-fatal tuberculosis developed.

SUMMARY

Since the initial 30-day period of treatment with streptomycin and para-aminosalicylic acid was not adequate to account for the improvement and subsequent recovery of this patient, it may be assumed that isoniazid, which was used alone thereafter, was the effective agent responsible for these developments. Ritchie, Taylor, and Dick7 have described the significant histological findings that lesions of miliary and meningeal tuberculosis undergo resolution with isoniazid while similar lesions treated with streptomycin fibrose. When these two drugs are used in combination the isoniazid effect predominates. The mortality rate and the incidence of neurological sequelae (from either meningitis or from treatment with intrathecal streptomycin) is still high with currently accepted antibiotic regimens. Until more is known about isoniazid in the treatment of miliary and meningeal tuberculosis the combination of isoniazid, streptomycin (intramuscular), and possibly para-aminosalicylic acid may be the regimen of choice. The present case has demonstrated marked therapeutic effect from isoniazid alone.

<table>
<thead>
<tr>
<th>Date</th>
<th>Cells</th>
<th>Culture for T.B.</th>
<th>Sugar</th>
<th>Chlorides</th>
<th>Proteins</th>
<th>Gold Sol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/8/52</td>
<td>16</td>
<td>Pos.</td>
<td>48</td>
<td>660</td>
<td>38</td>
<td>0000000000</td>
</tr>
<tr>
<td>4/16/52</td>
<td>154</td>
<td>Neg.</td>
<td>43</td>
<td>614</td>
<td>50</td>
<td>0122210000</td>
</tr>
<tr>
<td>5/7/52</td>
<td>25</td>
<td>Neg.</td>
<td>41</td>
<td>603</td>
<td>150</td>
<td>1233210000</td>
</tr>
<tr>
<td>5/20/52</td>
<td>18</td>
<td>Neg.</td>
<td>644</td>
<td>166</td>
<td></td>
<td>1233210000</td>
</tr>
<tr>
<td>6/14/52</td>
<td>19</td>
<td>Neg.</td>
<td>36</td>
<td>684</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>7/23/52</td>
<td>5</td>
<td>Neg.</td>
<td>53</td>
<td>705</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>9/10/52</td>
<td>0</td>
<td>Neg.</td>
<td>60.3</td>
<td>732</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>10/20/52</td>
<td>7</td>
<td>Neg.</td>
<td>62.0</td>
<td>727.5</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>11/20/52</td>
<td>6</td>
<td>Neg.</td>
<td>69</td>
<td>687</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/22/52</td>
<td>5</td>
<td>Neg.</td>
<td>59</td>
<td>762</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

RESUMEN

Puesto que el periodo inicial del tratamiento con estreptomicina durante 30 días asociados al PAS no fue adecuado para considerarlo como causa de la mejoría ulteriormente observada en este enfermo debe presumirse que se debió a la isoniazida que después fue usada solamente. Ritchie, Taylor y Dick7 han descrito los cambios histolóxicos significativos que sufren las lesiones de tuberculosis miliar y meningea en que son tratadas con isoniazida, se resuelven y cuando se tratan con estreptomicina hacen fibrosis. Cuando estas dos drogas se usan en combinación,
los efectos de la isoniazida predominan. La mortalidad y la incidencia de las secuelas neurológicas (sea de meningitis o por tratamiento con estreptomicina intratecal) es aún alta los regímenes de antibióticos aceptados. Hasta que se conozca más acerca de la isoniazida en el tratamiento de la tuberculosis miliar y meningea la combinación de estreptomicina, (intra muscular), isoniazida y quizás PAS, puede ser el régimen de elección. El caso que se presenta ha demostrado marcado efecto terapéutico por la isoniazida sola.

RESUME

Chez un malade, une période initiale de 30 jours de traitement par la streptomycine et le P.A.S. ne fut pas suffisante pour amélioration. Etant donné que la guérison fut obtenue ultérieurement, on peut penser que l'isoniazide seule utilisée par la suite, est responsable de cette évolution. Ritchie, Taylor et Dick ont décrit des constatations histologiques concluantes: des lesiones de tuberculosis miliaire et méninégée avaient finalement disparu sous l'influence de l'isoniazide, tandis que des lesiones semblables, traitées par la streptomycine s'étaient "fibrosées." Quand ces deux produits sont utilisés en association, l'effet de l'isoniazide prédomine. Le taux de mortalité et la fréquence des séquelles neurologiques (provenant soit de la méningite, soit du traitement par la streptomycine intrarachidienne) sont encore élevés les posologies antibiotiques couramment admises. Tant que nos connaissances ne seront pas plus approfondies au sujet de l'isoniazide dans le traitement de la tuberculose miliaire et méninégée, l'association isoniazida-streptomycine (intramusculaire) et eventuellement P.A.S. semble être le régime de choix. Le cas présenté démontre l'effet thérapeutique remarquable de l'isoniazide utilisée seule.

REFERENCES