DEAFNESS IN TUBERCULOUS MENINGITIS WITH A COMPARISON BETWEEN STREPTOMYCIN (CALCIUM CHLORIDE COMPLEX) AND DIHYDROSTREPTOMYCIN

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The successful clinical results obtained with dihydrostreptomycin in clinical and experimental tuberculosis and its comparative lack of neurotoxicity as reported by Edison et al. (1948), Feldman et al. (1948), Hinshaw et al. (1948) and Hobson et al. (1948) led to the general introduction of this drug into the therapy of tuberculosis. We have been using this drug since 1949, but in concert with other workers, Cathie and Garrow (1951) and Biagi (1951), have become aware of a worsening of our results and an increase in the number of deaf survivors. So much so that we have abandoned dihydrostreptomycin and reverted to streptomycin (calcium chloride complex).

It was felt therefore that a clinical comparison between these two drugs and an assessment of their effects on the cochlear and vestibular apparatus would serve a useful purpose.

Investigation

Since streptomycin was first used in Booth Hall Hospital, 66 cases of tuberculous meningitis have been treated. Of these, 38 have had streptomycin (calcium chloride complex) and 28 dihydrostreptomycin, with the above results.

The cases were entirely unselected and the longest period of survival has been three years four months and the shortest three months.

From Table I it can be seen that of the 36 streptomycin treated cases 25 (66 per cent.) have survived up till the time of writing, while of the 28 dihydrostreptomycin cases only 10 (36 per cent.) have survived.

It was highly suggestive, therefore, that the dihydrostreptomycin was responsible for these poor results but it was realized that other factors might have played a part such as:

(a) The presence or absence of miliary tuberculosis.

(b) The severity of the case on admission.

<table>
<thead>
<tr>
<th></th>
<th>No. Treated</th>
<th>No. of Survivors</th>
<th>No. of Deaf Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>38</td>
<td>25 (66%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>28</td>
<td>10 (36%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>35 (53%)</td>
<td>9 (26.4%)</td>
</tr>
</tbody>
</table>

*In receipt of a grant from the Medical Research Council.
(c) The dosage of streptomycin used and the method of treatment.

These possibilities were therefore investigated.

(a) Miliary Tuberculosis

The diagnosis of miliary tuberculosis was based on the characteristic 'snowstorm' appearance seen in the lungs radiologically or on the presence of tubercles in the choroid, and Table 2 shows the effect of miliary tuberculosis on the survival rates.

These results indicate: (1) That the chances of survival were less if miliary tuberculosis was present in addition to tuberculous meningitis, whichever drug was used. (2) That streptomycin was significantly more effective in the treatment of tuberculous meningitis with an associated miliary spread than dihydrostreptomycin.

(b) Severity of Case

The criteria of severity as suggested in the Medical Research Council Report on the Streptomycin Treatment of Tuberculous Meningitis (1948) were followed in classifying the severity of the disease.

Table 3 shows the results obtained.

These results show that there was no great difference in the degree of severity between the streptomycin treated cases and the dihydrostreptomycin cases.

(c) Dosage of Streptomycin and Method of Treatment

The method of treatment adopted in this hospital is as follows: 20 mgm. of streptomycin per lb. of body weight are given daily, divided into two doses given intramuscularly, as well as 1.5 mgm. per lb. body weight given intrathecally. This is continued for 90 days. If the cerebrospinal fluid returns to normal within that period then the intrathecal therapy is discontinued. A normal cerebrospinal fluid is classed as one with less than 10 cells per c.mm. and a steady protein. If the cerebrospinal fluid does not return to normal in 90 days then intrathecal therapy is continued on alternate days until normality is reached.

This method is used by the three paediatricians in charge of the cases and apart from minor variations treatment has been standardized.

Para-aminosalicylic acid is used in a proportion of cases and its effect on the ultimate result is shown in Table 4.

Surprisingly enough there is little difference in the survival rates when para-aminosalicylic acid was used in addition to the ordinary therapy. If anything, the results are a little better than the group treated without para-aminosalicylic acid.

Purified protein derivative was also given intrathecally in nine selected cases, all of them very ill or having signs of decerebrate rigidity. Four of these cases have survived. The two streptomycin treated cases survived while only two of the seven dihydrostreptomycin-treated cases survived. These results are too few to draw any conclusion as to the efficacy of purified protein derivative in the treatment of tuberculous meningitis.

Incidence of Deafness

From Table 1 it will be seen that not only was the mortality rate following dihydrostreptomycin higher than with streptomycin but there was an increase in the number of deaf survivors—six out of ten dihydrostreptomycin treated survivors became deaf (60 per cent.) as opposed to three out of twenty-five streptomycin treated survivors (12 per cent.). Two further dihydrostreptomycin treated patients...
who subsequently died were also deaf, making a total of 66 per cent. of all survivors at one stage.

Hearing Tests

To assess the form which the deafness took and to decide the stage in the disease at which it was likely to appear, one of us (P.G.) performed hearing tests at intervals throughout the course of the illness. Children of five years and over were given pure tone air conduction audiometric examinations at frequencies from 256 to 4,096, each ear being tested separately. Tests for children under five years consisted of pitch pipes covering speech range frequencies, drums, bells and other percussion instruments, the intensity of the sound being controlled by a sound level meter. The findings were confirmed by speech and voice tests of hearing, using phonetically balanced word lists and picture blocks which had been named previously by the child.

The following classification of hearing loss, based on the average loss in the better ear, covering the speech range of frequencies was adopted:

A—Losses of 15 to 30 decibels (minor hearing impairment).

B—Losses of 31 to 60 decibels (moderate partial deafness).

C—Losses of 61 to 80 decibels (severe deafness).

D—Losses of 81 to 90 decibels (very severe deafness).

E—Losses of 91 decibels and over (total deafness).

The numbers of survivors assigned to each of these grades is shown in Table 5.

Those whose hearing loss was over 60 decibels, that is in groups C, D and E, were unable to hear a voice at a distance of 1 ft. from either ear. None could benefit from the use of an individual hearing aid at the first time of testing because of amplification of lower frequency sounds. With highly skilled training children with a hearing loss in grades C and D might be able to use an aid at a later date provided there was no further deterioration in hearing capacity. The results showed a much severer hearing loss in those treated with dihydrostreptomycin than in the streptomycin treated children.

Audiograms of a child with tuberculous meningitis treated with dihydrostreptomycin are shown overleaf at the end of three months’ and six months’ therapy. These audiograms are representative of the others observed in this series and reveal an early severe deafness for high frequency sounds, and within three months of this appearing the lower frequencies are similarly affected.

Hearing loss for speech may appear suddenly and may even occur after treatment has been stopped, indicating that once impairment of hearing has occurred for high frequencies it tends to be progressive. The apparent suddenness in onset of the deafness is probably due to progressive hearing loss for frequencies in the speech range. Of significance are the experiments of Hawkins and Rahway (1948), who after injecting mice with streptomycin to tolerance limits and recording their result by the cathode ray oscilloscope, established that the higher frequencies were the first to be affected.

**Table 4**

**Effect of Para-Aminosalicylic Acid on Mortality Rates**

<table>
<thead>
<tr>
<th></th>
<th>No. Treated</th>
<th>No. given P.A.S. in addition to Streptomycin</th>
<th>No. who Survived</th>
<th>No. treated without P.A.S.</th>
<th>No. who Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>38</td>
<td>18</td>
<td>11 (61%)</td>
<td>20</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>28</td>
<td>18</td>
<td>6 (33%)</td>
<td>10</td>
<td>4 (40%)</td>
</tr>
</tbody>
</table>

**Table 5**

**Hearing Loss in Survivors**

<table>
<thead>
<tr>
<th>Drug Used</th>
<th>Hearing Loss Less than 15 Decibels</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>Total Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>19</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>
Of 97 cases of deafness referred to the Department of Education of the Deaf, Manchester University, since October 1949, following treatment of tuberculous meningitis, 18 were treated with streptomycin and 39 with dihydrostreptomycin.

**Relationship of Dosage to Deafness**

Accurate records of streptomycin dosage given are kept in this hospital and thus we have been able to calculate the total amount of streptomycin and dihydrostreptomycin given in each case, and it is therefore seemed worth while to attempt to relate the quantity given to the production of deafness.

The three deaf streptomycin treated survivors all had an intramuscular dose greater than 261.8 g., and a combined intrathecal and intramuscular dose greater than 270.3 g., while the non-deaf survivors had doses below this. However, the deafness does not seem to be directly related to the quantity of streptomycin given intracereally as a non-deaf survivor had 15 g. intrathecally while the highest intrathecal dose given to a deaf survivor was 8.5 g.

Turning to the dihydrostreptomycin treated cases, no such clear relationship can be established, while the lowest dose of dihydrostreptomycin which produced deafness was 85.7 g. intramuscularly, three of the non-deaf survivors had doses above this. Nor does the combined dose of intramuscular and intrathecal dihydrostreptomycin seem to bear any relationship to the deafness.

**Effects of Streptomycin on Vestibular Function**

One of the early claims for dihydrostreptomycin was its lack of neurotoxicity on the vestibular division of the eighth nerve. It was decided therefore to compare the effects of streptomycin and dihydrostreptomycin on the vestibular apparatus. However, it was soon found after a little experience that tests dependent on the observation of nystagmus, following caloric tests, e.g. Kobrak's test or turning tests, could not be applied to children owing to their failure to co-operate.

An attempt was made to devise a test which would be simple, could be applied to all ages and could be easily interpreted. The test was based on the simple physiological principle that rotation rapidly with the head in the upright position produces in normal people a subjective sensation of sham turning in the direction of rotation after the motion has ceased, stagger to the opposite direction of rotation when walking is attempted, and often a subjective sensation of nausea and visible pallor. Using this principle 30 children between the ages of three and 12, who were in hospital for conditions other than those involving the respiratory tract, were tested. Each child had an otological examination and those having a past history of otitis or otoscopic evidence of middle ear disease were excluded from the test. The child was first asked to walk along a straight line to ensure that co-ordination was normal. The eyes were then closed and while standing with the head in the erect position the child was turned in a clockwise and then an anti-clockwise direction at a
rate of one turn in 2 secs. He was then asked to open his eyes and walk along the line. The occurrence of stagger in a direction opposite to turning was accepted as evidence of normal vestibular function. The stagger was observed by two observers and both had to agree before the result was accepted.

The following results were obtained. When the children were turned five times in 10 secs., only five of the 30 children were noted to stagger. When 10 turns were made in 20 secs. stagger was produced in all children and a large proportion had subjective sensation of nausea with visible pallor. Failure to stagger after 10 turns in 20 secs. indicated impairment of vestibular function.

All survivors who had no residual neurological or physical disability were examined in this way. The test was carried out as before. The child was first tested for normal co-ordination by walking along a straight line, 10 turns being made in a clockwise direction in the standing position with the head erect and then in the opposite direction. The stagger was noted as before by two observers. If no stagger was produced by 10 turns, 20 were then performed in both clockwise and anti-clockwise directions. The younger children readily co-operated, especially if the test was made into a game, a toy being placed on a table at the end of a 10 ft. line and the child asked to fetch it. In the event of the child refusing to co-operate in the standing position he was merely placed on a stool with a rotating seat and turned the appropriate number of times in each direction. If no stagger was produced after 20 turns it was accepted that the labyrinth was grossly damaged.

From Table 6 it can be seen that 19 out of 20 of the streptomycin treated cases and four out of the six dihydrostreptomycin treated cases had evidence of labyrinthine disturbance. This shows a balance somewhat in favour of dihydrostreptomycin, but in view of the small number of cases tested this may not be significant.

Fortunately all children who had impairment of vestibular function were well compensated and only experienced unsteadiness in gait when walking along an irregular surface in the dark. The disadvantage of the test is that it can only be performed when the child is ambulant and thus cannot be applied early in the illness, and the child must have no physical defect which would interfere with the performance of the test.

**Discussion**

It appears that the results obtained with dihydrostreptomycin were inferior to streptomycin in the treatment of tuberculous meningitis. Surprisingly enough para-aminosalicylic acid did not make any contribution to a reduction in the mortality rate, especially in view of the report of Daniels and Hill (1952) who showed better results with streptomycin and dihydrostreptomycin combined with para-aminosalicylic acid than either drug alone in young adults with pulmonary tuberculosis.

Many workers have recorded an increase in the incidence of deafness following treatment of
tuberculous meningitis with dihydrostreptomycin. Kahl (1951) has reported three cases of deafness in 31 survivors treated with streptomycin, while of 13 survivors treated with dihydrostreptomycin six were deaf. He concludes that dihydrostreptomycin has a considerable toxic effect on the eighth nerve. Giraud et al. (1951) also noted 15 cases of deafness in 71 dihydrostreptomycin treated survivors but only five in 130 streptomycin treated survivors. Similar results were reported by Beyer et al. (1951) who found two cases of deafness in 51 survivors treated with streptomycin but when dihydrostreptomycin was used, seven cases of severe deafness and five of diminished hearing occurred in 15 survivors. Biagi (1951) in this country has also had worse results with dihydrostreptomycin and found four cases of deafness in eight survivors, while Calnan et al. (1951) had only two cases of deafness in 16 surviving streptomycin treated cases but all had impairment of vestibular function. Kluyskens et al. (1950) believe that if treatment is stopped as soon as hearing loss in the high frequencies is noted, no further deterioration occurred. This is not always the case as in one patient in our series deafness progressed into speech frequencies in spite of cessation of treatment. Hobson et al. (1948) found that deafness first appeared on the 30th day of treatment after 150 g. of dihydrostreptomycin had been given intramuscularly, but they maintain that dihydrostreptomycin was no more toxic than streptomycin in this respect. In our series deafness occurred when a total of 261.8 g. of streptomycin had been given intramuscularly, but in the dihydrostreptomycin treated group no correlation between the dosage and deafness produced could be shown.

Once deafness has occurred no improvement takes place and it appears that the damage to the cochlear division of the eighth nerve is irreversible. If speech deterioration is to be avoided, frequent audiometric tests should be performed during the course of the illness, and as soon as hearing loss is noted, the child should be placed for training with a teacher of the deaf, even while still having treatment.

These deaf children present special social and psychological problems on discharge from hospital. An aural rehabilitation centre would be ideal, where they could be taught to lip read and use their residual hearing under the best conditions. This would be a preliminary to returning them to a school for normal children or elsewhere according to the degree of their disability.

Disturbance of the labyrinth did not constitute a severe disability and appeared in the majority of our cases whether treated with streptomycin or dihydrostreptomycin. Fowler and Feind (1949) believe that this is a function of the dosage, as on 4 g. of streptomycin per day 98 per cent. of the patients developed impairment on the sixth to tenth days while on 1 g. per day labyrinthine disturbance developed about the 60th day, and Brown and Pfuetze (1948) stated that disturbance in equilibrium will occur if the dosage of streptomycin is 1 to 2 g. per day or more. Hobson et al. (1948) believe that dihydrostreptomycin is less neurotoxic than streptomycin and the first appearance of labyrinthine dysfunction was on the 32nd day of treatment when the patient was receiving 3 g. of dihydrostreptomycin per day. Hinshaw et al. (1948) are also of the same opinion as when using dihydrostreptomycin only one patient out of 14 had vestibular damage on 2.8 g. per day for eight days. Our own experience has been that dihydrostreptomycin was only slightly less toxic to the vestibular division of the eighth nerve than streptomycin. But this is far outweighed by its greater damage to the cochlear apparatus and the very poor survival rate.

Summary

The results of streptomycin (calcium chloride complex) and dihydrostreptomycin in the treatment of 66 cases of tuberculous meningitis have been compared and it was found that streptomycin was significantly more effective.

The presence of miliary tuberculosis reduced the chances of survival.

There was little difference in the mortality rates
when para-aminosalicylic acid was used in addition to streptomycin and dihydrostreptomycin.

The incidence of deafness in the dihydrostreptomycin treated group was higher than in the streptomycin treated group.

Deafness in the streptomycin treated patients occurred after 261.8 g. intramuscularly and after a combined intrathecal and intramuscular dose of 270.3 g. No correlation between deafness and dosage in the dihydrostreptomycin treated group could be established.

Vestibular damage occurred in 19 out of 20 streptomycin treated cases and in four out of six dihydrostreptomycin treated cases.

It is suggested that speech training facilities be provided for children as soon as high frequency deafness is noted and that a special aural rehabilitation centre should be established.

We wish to thank Professor A. G. W. Ewing, Director, Department of Education of the Deaf, University of Manchester, and Dr. W. H. Patterson, Superintendent, Booth Hall Hospital, for their advice and criticisms and Dr. S. K. Guthrie, Dr. W. H. Patterson and Dr. M. L. Thomson for permission to use their cases, and especially the Nursing Staff at Booth Hall Hospital on whom the burden of nursing these children has fallen.

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