Apparent Cerebral Atrophic Findings on Cranial Computed Tomography in Nephrotic Children with Steroid Therapy and in Patients of Infantile Spasms with ACTH Therapy

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Summary: This study examined the influence of corticosteroids and ACTH on the brain of patients with nephrotic syndrome and infantile spasms by means of cranial computed tomography (CCT).

CSF-space/intracranial space (C/I) ratio was used as a parameter of apparent cerebral atrophic findings, that is, the enlargement of the ventricles and the subarachnoid space. C/I ratio was calculated by computer processing of CCT at the level of the 3rd and lateral ventricles. This is the first report in which computer processing is applied to the evaluation of CCT findings to study the effects of steroids and ACTH on the brain.

Twelve of fifteen nephrotic patients showed abnormal C/I ratio after intensive steroid therapy. The average dose was 2147 mg of prednisolone for 3 weeks to 5 months. The average C/I ratio in the fifteen patients was 6.6 ± 3.9 % compared with 1.6 ± 0.8 % in 34 control individuals. The C/I ratio in the twelve patients with abnormally high values decreased to 2.6 ± 1.5 % after reduction or withdrawal of steroids. The C/I ratio returned to normal in 9 of 12 patients at that time.

In all patients treated with ACTH, C/I ratios increased significantly during ACTH therapy. In 8 patients with infantile spasms, C/I ratios were 5.1 ± 3.9 % before, 16.4 ± 7.8 % during, and 6.2 ± 3.3 % between 2 and 20 months after the withdrawal of therapy (0.25 to 0.5 mg/day of ACTH, IM., for 2 to 3 weeks).

Although apparent cerebral atrophic findings were reversible in these patients, the data suggests that corticosteroid and ACTH can cause morphological changes of the cerebra in children as evaluated by CCT. The long-term and massive administration of steroids or ACTH should be minimized in children with growing cerebra, especially in neonates and infants.

Key words: nephrotic syndrome — infantile spasms — steroid therapy — ACTH therapy — cranial computed tomography — apparent cerebral atrophy

Introduction

Since the time steroids were introduced by Hench and Kendall in 1948, with dramatic effects, to the treatment of rheumatic disease, it has been widely recognized that in many diseases both ACTH and adrenal cortical hormone are highly effective for treatment. Recently the side-effects of these hormones on the central nervous system such as psychosis, seizure and neuropathy have been discussed. Their pathophysiological mechanisms remain unknown, however.
Apparent cerebral atrophic findings on CCT is defined as enlargement of the ventricular and subarachnoid space. This findings has been related to the use of corticosteroids. This study examined the influence of steroids and ACTH on the cerebra of children by using CCT during the course of corticosteroid and ACTH therapies in patients with nephrotic syndrome and infantile spasms, respectively.

**Material and Methods**

Patients were divided into 3 groups; the nephrotic patients treated with steroids, the infantile spasm patients treated with ACTH and the controls who received neither steroids nor ACTH.

Group 1: The subjects were 2 to 12 year old nephrotic patients, including 8 males and 7 females, who were admitted to the pediatric ward of Kurume University Hospital during the period from January, 1977 to July, 1980. All but one were treated with prednisolone in an average dose of 2147 mg for 3 weeks to 5 months. The following histological diagnosis of the patients' renal lesions were made: minimal change in 11, proliferative glomerulonephritis in 3, and chronic sclerosing in 1. CCT was performed at least twice during the course of steroid therapy; at the end of 4 weeks of continuous daily administration of 60 mg/SA/day of prednisolone and during maintenance therapy. In three patients, CCT was obtained before initiation of steroid therapy.

Group 2: The subjects were 5 male and 3 female patients with infantile spasms, age 2 months to 2½ years, who were admitted to the pediatric ward during the period from October, 1977 to April, 1980. These patients had CCT during the course of ACTH therapy (0.25 to 0.5 mg/day for 2 to 3 weeks).
Group 3: As a control, 34 patients who had febrile convulsion or headache with apparently normal CCT, were used. Their ages ranged from 5 months to 18 years.

An EMI scanner (160×160 matrix) was used in our examination. For the computer processing, we used 4 slices of CCT containing most of the 3rd ventricular and all of the lateral ventricles of the brain (Fig. 1). In order to quantify the results obtained from our investigation, CSF-space/intracranial space ratio (C/I ratio) was calculated as a parameter of apparent cerebral atrophic findings after employing smoothing procedures by a YHP-21-MX-2100 computer (Hewlett Packard Inc.).

Results

I. C/I ratios in nephrotic patients treated with steroids.

The average C/I ratio in 15 nephrotic patients during steroid therapy was 6.6 ± 3.9 % (M ± S.D.), while the ratio in the 34 controls was 1.6 ± 0.8 %. These data are presented in Fig. 3. C/I ratios higher than the mean ± 2 S.D. of the control group were found in 12 (80 %) of the 15 patients, with an average C/I ratio of 7.5 ± 3.9 %. Of the 12 patients, markedly elevated C/I ratios (17.3 % and 10.6 %) were found in two, moderately elevated (5 - 10 %) in 7, and minimally elevated (3.5 - 5 %) in 3 patients (Table 1). No significant difference in steroid dose or duration of steroid therapy was found between groups with normal and abnormal C/I ratios. The C/I ratio in the 12 nephrotic patients during steroid therapy was 7.5 ± 3.9 %. However, after reduction or withdrawal of steroids, the ratio returned to normal in 9, and decreased in 3 patients in whom the mean C/I ratio was 2.6 ± 1.5 %.

Of the 15 nephrotic patients in this...
Fig. 4. The C/I ratio in 12 of 15 nephrotic patients who had abnormally high ratios (7.5 ± 3.9 %) changed to 2.6 ± 1.5 % after the reduction or withdrawal of steroid. Nine of twelve patients returned to a normal C/I ratio.

### TABLE 1

*Dose and Duration of Steroid and Maximum C/I Ratio in Nephrotic Patients*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Dose (mg)</th>
<th>Duration (months)</th>
<th>Maximum C/I R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. D. H.</td>
<td>9</td>
<td>1800</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>2. K. K.</td>
<td>6</td>
<td>1050</td>
<td>1</td>
<td>8.9</td>
</tr>
<tr>
<td>3. I. K.</td>
<td>8</td>
<td>1500</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>4. Y. K.</td>
<td>6</td>
<td>1800</td>
<td>1</td>
<td>3.4*</td>
</tr>
<tr>
<td>5. I. T.</td>
<td>9</td>
<td>1800</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>6. K. H.</td>
<td>7</td>
<td>1500</td>
<td>1</td>
<td>5.8</td>
</tr>
<tr>
<td>7. U. K.</td>
<td>6</td>
<td>1500</td>
<td>1</td>
<td>2.7*</td>
</tr>
<tr>
<td>8. K. K.</td>
<td>2</td>
<td>1050</td>
<td>1</td>
<td>8.2</td>
</tr>
<tr>
<td>9. S. K.</td>
<td>5</td>
<td>1350</td>
<td>1</td>
<td>10.6</td>
</tr>
<tr>
<td>10. S. K.</td>
<td>4</td>
<td>1350</td>
<td>2.5</td>
<td>17.3</td>
</tr>
<tr>
<td>11. K. R.</td>
<td>12</td>
<td>8550</td>
<td>5</td>
<td>8.0</td>
</tr>
<tr>
<td>12. U. Y.</td>
<td>7</td>
<td>2250</td>
<td>1 + 1</td>
<td>5.2</td>
</tr>
<tr>
<td>13. E. M.</td>
<td>8</td>
<td>4350</td>
<td>1 + 3.5</td>
<td>2.9*</td>
</tr>
<tr>
<td>14. A. Y.</td>
<td>12</td>
<td>1760</td>
<td>1 + 1</td>
<td>8.2</td>
</tr>
<tr>
<td>15. A. T.</td>
<td>5</td>
<td>420</td>
<td>1wk + 2wks</td>
<td>3.8</td>
</tr>
</tbody>
</table>

* normal C/I R.
study, 2 exhibited manic behavior, 1 exhibited a depressed state, 4 experienced muscle weakness, and 1 experienced finger tremor. These symptoms were of moderate degree and there was no relationship between the symptoms and degree of cerebral atrophic findings on CCT.

Case Histories

1. Patient No. 10 (Fig. 5) S. K. 4 year old male ($\#$ 78 - 1740)

The patient developed edema of the face and extremities on April 8, 1978. He was treated with continuous administration of paramethasone in a daily dose of 6 - 8 mg and betamethasone in a daily dose of 1.5 - 2 mg for 2 1/2 months under the diagnosis of nephrotic syndrome. His condition did not improve, and he was referred to this hospital when side-effects of the steroids developed, including: moon face, hypertrichosis, manic reaction, muscle weakness, high blood pressure and osteoporosis. These side-effects gradually disappeared with dose reduction. CCT findings on admission showed significant enlargement of cerebral ventricles and sulci with a C/I ratio of 17.3%, the highest level in the present series. IQ level was 116 (Tanaka-Binet model) and there were no neurological abnormalities.

One month after the dose of prednisolone was reduced, the ratio had improved to 13.2%. The cerebral ventricles and sulci were restored to normal size after almost ten months. In spite of the cerebral changes, no EEG abnormalities were found and no neurological abnormalities were noted.

2. Patient No. 1 (Fig. 6) D. H. ($\#$ 77-3776)

This patient, a 9 year old male, developed edema of the eye lid in December, 1977. After prednisolone in a daily dose of 60 mg/SA was administered for 4 consecutive weeks, CCT findings revealed moderate enlargement of the cerebral ventricle and sulci with a C/I ratio of 5.6%. Two months after the dose of prednisolone was reduced, the CCT findings returned to normal (2.8%). Prednisolone was increased to a daily dose of 60 mg/SA after a clinical relapse and enlargement of the cerebral ventricles and sulci (C/I ratio = 4.0%) was detected by CCT one month thereafter.

3. Patient No. 11 (Fig. 7) K. R. ($\#$ 76-2038)

A 12 year old female developed edema of the face and head in February, 1976. She was admitted in August because her symptoms had worsened and she received a daily dose of 60 mg/SA for 4 consecutive weeks. Five months after the initiation of steroid therapy, the CCT findings showed enlargement of cerebral ventricles and sulci (C/I ratio of 8.0%). But C/I ratio returned to a normal level one year after steroids were discontinued.

II. C/I ratio in infantile spasms treated with ACTH

C/I ratios in eight patients with infantile spasms given ACTH were evaluated by the same method. The C/I ratio increased during ACTH treatment, but tended to recover gradually after withdrawal of treatment (Fig. 8). All patients were found to be abnormal, with a C/I ratio of 16.4 ± 7.8% during ACTH therapy. This value is significantly higher than the pre-treatment level of 5.1 ± 3.9% (P<0.01). Before therapy, 3 of 7 patients showed abnormally high C/I ratios. There was also a significant difference in the C/I ratio during ACTH therapy and that obtained 2-20 months after withdrawal of ACTH (P<0.05) (Table 2).

Two patients' C/I ratio increased with additional prednisolone therapy (patients: S. E. and T. I. Fig. 8).
Patient S. K. 4 yrs M. (#78-1740)

1978. 7. 11

Fig. 5. Scans obtained during steroid therapy revealed significant widening of CSF spaces with a C/I ratio of 17.3%. CCT study after the discontinuation of steroid therapy demonstrated a marked reduction in size of ventricles, sulci and cisterns.
Patient D.H. 9 yrs M. (ID 77-3776)

1978. 2. 9

CSF-space/Intracranial space (%)

1978. 4. 4

5.6

1978. 10. 16

2.8

4.0

Fig. 6. CCT findings showed a moderate enlargement of the cerebral ventricles and sulci with a C/I ratio of 5.6% after steroid therapy and returned to normal after the reduction of steroid. However, CCT study showed widening of CSF spaces after prednisolone dose was increased for the relapse.
Case Histories

1. Patient No. 3 (Fig. 9) S. T. (#77–3091)
   This 6 month old female developed infantile spasms of unknown origin at 4 months of age. Hypsarrythmia was confirmed by EEG taken when she was admitted at the age of 6 months. Although seizures were initially controlled by administration of ACTH at a daily dose of 0.25 mg given for 3 consecutive weeks, the seizure recurred. Her neurological development has been significantly affected; her DQ was 12 at 3 years of age. The patient’s C/I ratio was almost normal before ACTH treatment was begun. However, the ratio worsened from 3.4% to 21% after one month of therapy. The C/I ratio remained abnormal 1½ year later, during a follow-up examination.

2. Patient No. 1 (Fig. 10) S. E. 5 month old male (#77–3322)
   Myoclonus of the eyelid was noticed in this patient on the first day of life. When he was 3 month old, pachygyria was confirmed by pneumoencephalography and diagnosis of infantile spasms was made at 5 months of age. The C/I ratio was 9.5%.

   After administration of ACTH, the ratio rapidly shifted to 30.2%, and enlargement of the cistern of the frontal and temporal lobes was especially marked. However, his CCT findings had returned almost to pre-ACTH therapy level when examined at 1 year 9 months after cessation of ACTH therapy. Prednisolone in a dose of 2–3 mg/kg was administered because the convulsions could not be controlled. The C/I ratios increased from 7.2% to 15.0% again.
TABLE 2
Dose of ACTH-Z and C/I R. in 8 Patients with Infantile Spasms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (months)</th>
<th>Aetiology</th>
<th>ACTH-Z</th>
<th>C/I R. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose (mg)</td>
<td>Duration (w)</td>
</tr>
<tr>
<td>1. S. E.</td>
<td>5</td>
<td>Pachygyria</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>2. M. H.</td>
<td>1</td>
<td>Perinatal hypoxia</td>
<td>0.25</td>
<td>3</td>
</tr>
<tr>
<td>3. S. T.</td>
<td>5</td>
<td>Cryptogenic</td>
<td>0.25</td>
<td>3</td>
</tr>
<tr>
<td>4. T. I.</td>
<td>5</td>
<td>Cryptogenic</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>5. H. S.</td>
<td>6</td>
<td>Cryptogenic</td>
<td>0.25</td>
<td>3</td>
</tr>
<tr>
<td>6. K. Y.</td>
<td>7</td>
<td>Premature</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>7. T. K.</td>
<td>10</td>
<td>Meningitis</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>8. E. K.</td>
<td>2 yrs 7 mths</td>
<td>Cryptogenic</td>
<td>0.5</td>
<td>2</td>
</tr>
</tbody>
</table>

FOLLOW-UP CT STUDY BY YHP-COMPUTER ANALYZING 8 CASES OF INFANTILE SPASMS

— Change in CSF-space/intracranial space (%) and months after ACTH therapy —

*Fig. 8.* The C/I ratio increased during ACTH treatment, and gradually returned to normal after withdrawal.
Fig. 9. CSF spaces were of normal size before ACTH therapy. Scans obtained during ACTH therapy showed severe sulcal and cisternal widening. The C/I ratio had rapidly worsened from 3.4 % to 21 %.
Patient S. E. M. (#77-3322)

Fig. 10. Pachygyria was confirmed by pneumoencephalography at 5 months of age. A laterality of the cerebral ventricles was noted in the CCT findings. The C/I ratio rapidly shifted from 9.5% to 30.2% during ACTH therapy.
Discussion

1. Effects of steroids and ACTH on the brain.

Evaluation of C/I ratio by CCT revealed that 12 of 15 nephrotic patients given massive doses of steroids developed enlargement of the cerebral ventricles, cisterns, sylvian fissure and interhemispheric fissure in varying degrees. No significant correlation was found among steroid dose, duration of steroid therapy, and C/I ratio. Follow-up CCT study on twelve patients showed that the increased C/I ratios had returned to normal in 9 of 12 patients when the steroid dose was reduced or discontinued.

We found the same pattern in the patients with juvenile rheumatoid arthritis and myasthenia gravis who were treated with prednisolone. Similarly, Bentson et al. (1978) have reported transient cerebral atrophy documented by CCT in 15 patients with autoimmune diseases such as systemic lupus erythematosus who were treated with steroids.

Gastaut et al. (1978) reported that of 37 children with infantile spasms only seven had a normal CCT and the remaining 30 (81%) showed abnormal findings. In 22 of the 30 patients with cerebral lesions, global cortical-subcortical atrophy was observed. But the authors did not mention any correlation between CCT abnormalities and ACTH therapy in their study. It seems that ACTH can cause reversible cerebral changes, as demonstrated by C/I ratio in our study. Lagenstein et al. (1979) obtained similar results with ACTH treatment in patients with petit mal epilepsy, West syndrome and Lennox syndrome.

2. Mechanisms of steroid action on CNS.

Authors have suggested two different mechanisms to explain the pathogenesis of apparent cerebral atrophic findings caused by steroid or ACTH therapy. Momose et al. (1971) performed pneumoencephalography on 31 patients varying in age from 18 to 66 years old with Cushing syndrome, and reported cortical atrophy of both cerebral and cerebellar hemispheres. All patients with cerebral cortical atrophy exhibited irritability, nervousness, memory deficit, hallucination and changes of mood, but no cerebellar symptoms were found. The severity of the cerebral or cerebellar cortical atrophy did not correlate with the duration of the disease. Such atrophy could be related to the severity of the disease, judged by clinical findings including: thinning of the skin, muscle wasting, atrophy of the blood vessels, and osteoporosis, all of which are caused by progressive protein catabolism. The severity of the clinical condition of 4 patients with muscle weakness in our study, however, did not correlate with the severity of CCT findings.

Another possible explanation for such cerebral atrophy is a reduction in brain weight due to loss of water. In normal rats given dexamethasone, water levels decreased at 24 or 48 hours, and brain sodium and potassium concentrations increased slightly at 72 hours (Siegel et al., 1972). Timiras et al. (1954) obtained the same results from experiments performed on mice. Such findings have been supported by numerous reports which confirmed the effects of steroids in experimental brain edema (Ruelen et al., 1969, Yamaguchi et al., 1975). However, Taylor et al. (1964) reported that no significant changes were noted in water and electrolyte concentrations 6 days after dexamethasone was given to healthy rabbits. Thus, no established theory exists to explain the mechanism of steroid action in the central nervous system. This problem needs further study.

3. Prognostic significance for the evaluation of effects on intelligence.
Despite abnormal CCT findings, no significant influence of steroids on the intelligence of the nephrotic patients was seen, and no problems were found after steroid therapy was discontinued. One nephrotic patient (patient No. 10), who revealed marked cerebral changes on CCT, was normal with IQ 116 (Tanaka-Binet model) after steroid therapy. As for the long-term prognosis of patients with infantile spasms given ACTH, Suzuki et al. (1977) and Jeavons et al. (1973) reported that there was no significant difference in the long-term prognosis of infantile spasm patients irrespective of whether they were treated with ACTH or steroids. We did not form a conclusion on this matter because of the relatively few patients in our study. However, in view of the fact that CCT findings in children treated with ACTH were reversible and identical to those of nephrotic patients with steroid therapy, it would seem that the effect on intelligence is probably not serious.

Long-term high doses of ACTH have been given recently for seizure control (Singel et al., 1980). Because patients with infantile spasms are treated during the growing stage of cerebral function, extra caution should be paid in clinical practice. A series of experimental data concerning the influences of cortisone and ACTH on brain development have been recently reported. Howard (1965) found a reduced brain and body weight in neonatal mice after steroid administration. Gumbinas et al. (1973) reported a decrease in frequency of myelinated fibers and a decrease in number of lamellae for a given axon circumference, which did not improved with age. Palo and Savolainen (1974) reported that both body and brain weights were significantly reduced when high doses of the synthetic ACTH were given to 2 week old rats. Finally, Howard (1974) reported that mice given a single large dose of corticosterone at 2 days of age showed lasting alterations in operant behavior associated with reduction in cerebral weight and DNA content when tested as adults. But when mice were given corticosterone at 22 days, no changes appeared in cerebral weight, DNA or in operant behavior. Therefore, the long-term and massive administration of steroids or ACTH should be minimized in children with growing cerebra, especially in neonates and infants.

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