ACTH therapy in infantile spasms: side effects

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SUMMARY 162 children with infantile spasms were treated with ACTH at the Children's Hospital, Helsinki, and at the Aurora Hospital, Helsinki, during 1960–76. In a large proportion (37%) of the children the treatment caused pronounced side effects, and the mortality was 4.9%. The most common complications were infections: septic infections, pneumonias, and urinary and gastrointestinal infections. Other side effects were arterial hypertension (11), osteoporosis (2), hypokalaemic alkalosis (2), and other marked electrolyte disturbances (10). In 2 children necropsy showed fresh intracerebral haemorrhages. Four children developed oliguria and hyperkalaemia during and after withdrawal of ACTH. One of them had tubular necrosis confirmed by renal biopsy. Infections were significantly more common with large doses (120 units) of ACTH than with small ones (40 units). It is concluded that side effects, even severe ones, are more common during this treatment than had been assumed. Careful watch is important before and after treatment. The benefit of very high dosages should also be reconsidered.

For 20 years ACTH or corticosteroids has been the treatment of choice in infantile spasms.¹ Although there are conflicting observations about whether or not it affects intellectual outcome^{2–8} it usually stops the seizures, and there are fewer relapses than after conventional anticonvulsive drugs. Primarily, spasms will be controlled in 60 to 80% of the children.^{9–12}

Daily dosage varies from 20 to 180 units and the duration of treatment from 3 weeks to 6 months. Some give ACTH alone. Others combine it with glucocorticoids, generally with dexamethasone or prednisolone. Despite large doses and long duration, side effects have been considered slight or they have not been carefully investigated.^{5 11–13} However, severe side effects and fatal results from treatment with ACTH and dexamethasone have been reported from Germany.^{2 14–15} Sorel¹⁶ noted that side effects were associated with the use of synthetic ACTH. In our large series^{17–18} treatment with ACTH appeared to cause frequent and sometimes severe side effects.

Materials and method

In 1960–76 at the Children's Hospital, University of Helsinki, and the Aurora Hospital, Helsinki, 162 children with infantile spasms at the mean age of 9.4 (range 1–32) months were treated with long-acting ACTH. Corticotrophin (Acton prolongatum, Acortan prolongatum, Cortrophin Z) was used in 139 patients, its synthetic analogue Zn tetracosactrin (Synachten Depot, S-Cortrophin Depot) in 23

patients. ACTH was given once a day intramuscularly. In 97 children the daily dosage was 40 units for 3 weeks, 20 units for 2 weeks, and then it was gradually stopped in 1 week. After 1969 larger doses were used. 54 children had daily 120–160 units for 3 weeks, 60–80 units for 2 weeks, and then it was gradually stopped in 1 week. 11 of the 162 children were treated with ACTH and dexamethasone. ACTH was gradually increased to 80 units a day and this was maintained for 3 weeks or longer if there was no clinical response. After the response the dose was reduced and treatment was continued intermittently with dexamethasone—that is 4–9 mg once a day for 4 days followed by 6 days without. This treatment was continued for 3–4 months and during this time the children stayed on noninfectious paediatric wards. Before starting treatment with ACTH each child was examined to exclude infections by examinations of urine, erythrocyte sedimentation rate and blood cell count, bacterial cultures from nose, throat, and urine, and x-rays of the lungs. 10 children received no ACTH, because they had resistant infections (3 had cytomegalovirus) and ACTH was considered to carry too great a risk for them. 42 children had been severely retarded since birth or had severe malformations and they were not treated with ACTH since it could not benefit them. Thus, there was some selection for treatment of 214 children admitted with infantile spasms during 1960–76. These 52 children were given conventional anticonvulsants.

Results

60 (37%) children showed pronounced side effects. In 24 (14.8%) the side effects were severe or fatal. Eight (4.9%) died during ACTH treatment or after complications of the treatment (Table 1). In none of them was there any minor respiratory infection or minor side effect of hypercortisolism—such as steroid acne, or weight gain and 'moon face'.

With larger dosage of ACTH (usually 120 units), 42.6% (23/54) of children had pronounced side effects. With the smaller dosage (40 units) 35% (34/97) had side effects. During treatment with ACTH and dexamethasone combined 27.3% (3/11) had side effects. When synthetic analogues of ACTH were used 69.6% (16/23) had side effects. There were more infections with large doses ($P < 0.05$; $\chi^2 = 4.474$) and with synthetic analogues of ACTH

(NS; $\chi^2 = 3.294$). The number of infections was significantly increased with larger doses.

Infections. Five patients had septic infections during treatment with ACTH, 3 of whom died. Blood cultures showed *Staphylococcus aureus* (2), *Klebsiella pneumoniae* (1), *Escherichia coli* (1), and *Proteus vulgaris* (1). Some other children were suspected to have sepsis, but no blood cultures were made. 20 had pneumonia, 6 of whom died (3 who had a simultaneous sepsis are in this category). In 2 children who died of pneumonia the micro-organism responsible was *Pneumocystis carinii*.

One child who died had a generalised cytomegalovirus and staphylococcus. His lungs, kidneys, liver, and hypophysis were affected by cytomegalovirus. Another child developed a staphylococcal empyema, which was cured by lung drainage and antibiotics.

Table 1 Lethal outcome of ACTH therapy, 8 cases

Case	Aetiology of infantile spasms	Treatment	Age (months)			Necropsy		
			At start of treatment	At death		Combined weight of adrenal glands (g)	Normal weight (g)† SD	Micro-organism
1	Neonatal hypoglycaemia	Corticotrophin, 40 units/day 6 weeks	5½	7	Massive bleeding into the right cerebral ventricle*	13.5	5.5 ± 2.2	Not examined
2	Familial encephalopathy	Corticotrophin, 40 units/day 3 weeks	5	6½	Lobar pneumonia. Big thrombus of dural sinus	Not examined		Not found
3	Neonatal hypoglycaemia	Corticotrophin, 30 units/day 6 weeks	5½	7	Interstitial pneumonia. Subarachnoid haemorrhage on the right hemisphere	6.5	5.5 ± 2.2	<i>Pneumocystis carinii</i>
4	Prenatal lesion	Zn tetracosactrin, 0.2 mg/day 4 weeks	2	3	Purulent pneumonia	12.5	4.8 ± 1.4	<i>Escherichia coli</i>
5	Idiopathic	Zn tetracosactrin, 0.3 mg/day 5 weeks	3	4½	Sepsis. Pneumonia. Cytomegalovirus. Moniliasis	10.5	4.6 ± 2.1	<i>Staphylococcus aureus</i> . <i>Candida</i> . Cytomegalovirus
6	Neonatal hypoglycaemia	Corticotrophin, 120 units/day 6 weeks	7½	9	Purulent pneumonia	10	5.4 ± 1.5	<i>Klebsiella pneumoniae</i>
7	Brain malformation	Corticotrophin, 120 units/day 6 weeks	5	6½	Interstitial pneumonia. Microgyric brain	8.5	4.6 ± 1.5	<i>Pneumocystis carinii</i>
8	Familial	Corticotrophin, 120 units/day 6 weeks	3	7	Pneumonia	20	5.5 ± 2.2	Not found

*At start of treatment with ACTH the cerebrospinal fluid was normal.

†Normal weight of organs, according to Schulz *et al.*⁴²

Table 2 Infections during treatment with ACTH

Treatment	No of children treated	Children with infections		Children with septic infections	
		No	%	No	%
Lower doses (20–40 units per day)	97 (4) ^s	22*	22.7	5	5.2
Larger doses (120–160 units per day)	54 (5) ^s	21	38.9	1	1.8
ACTH and dexamethasone combined	11 (1) ^s	2	18.2	—	—
Synthetic ACTH	23	10	43.5	2	8.7

^s Number of children with synthetic ACTH.

*— $P < 0.05$, $\chi^2 = 4.474$.

One child (Case 1) was exposed to tuberculosis during treatment with ACTH. Perhaps her death at age 13 months was due to this infection.

Case 1

The girl did not have the conventional BCG vaccination during the neonatal period because she had convulsions from age 2 days. Later she developed infantile spasms and was treated with ACTH at age 2 to 3 months. During her stay in hospital she came in contact with a person with cavitating tuberculosis. At age 5 months primary tuberculosis of the lungs was diagnosed and 8 months later she died despite anti-tuberculous therapy. The diagnosis was confirmed at necropsy.

Urinary infections developed during ACTH therapy in 11 patients. One child had a fulminant *Proteus mirabilis* infection, peritonitis, and uraemia after 2 weeks' therapy with corticotrophin. A purulent infection developed in the right hydro-nephrotic kidney (detected later by intravenous urography).

One child had a severe and protracted cytomegalovirus infection during treatment with ACTH: meningoencephalitis with fever for many months, and a rise in the erythrocyte sedimentation rate to more than 100 mm/h. At age 6 years the girl still had pathological CSF findings (high IgG: albumin ratio), which may indicate local production of immunoglobulins in the central nervous system and be interpreted as a sign of a slow virus infection.¹⁷

Other infections. 10 children had gastroenteritis. Two of them required intravenous rehydration. One child was severely ill and the infection lasted 2 weeks. Candida infections of the oral mucosa were common. In 3 cases the infection was fulminant, in one it extended from the mouth to the larynx, intestines, and lungs.

Four children later had recurrent infections—for example, one of them had 10 attacks of pneumonia and 16 attacks of febrile bronchitis during his lifespan of 7 years. Minor infections were skin abscess (1), furunculosis (1), otitis (2), and fever of unknown origin (4). The role of ACTH in these cases remains obscure.

Hypertension. 11 of the 17 children examined had arterial hypertension, which generally developed in the 2nd or 3rd week of ACTH treatment. The blood pressure was raised in these 11 children—to 160/110, 180/130, 280/150, 200/90, 210/150, 140/100, 160/100, 165/100, 130/100, 210/160, 190/100 mmHg. One child also had hypertensive ophthalmoscopic findings: strong general arterial narrowing in the fundi. Unfortunately, blood pressure was not

measured routinely. After treatment the blood pressure was normal in these children.

Intracerebral haemorrhage. In one case the cause of death was fresh intraventricular cerebral haemorrhage and in another necropsy showed fresh subarachnoid haemorrhage and interstitial pneumonia. The cause of the bleeding remained unknown—for example blood pressure had not been examined.

Osteoporosis. Two children developed osteoporosis during treatment with ACTH. One child had slightly subnormal serum calcium even before therapy (2.00–2.4 mmol/l; 8–9.6 mg/100 ml) but after 2 weeks' therapy both calcium and phosphate levels were low (calcium: 1.3–1.65 mmol/l; 5.2–6.6 mg/100 ml and phosphate: 1.16–1.65 mmol/l; 3.6–5.1 mg/100 ml), normal calcium 2.15–2.7 mmol/l (8.6–10.8 mg/100 ml) and normal phosphate 1.50–2.50 mmol/l (4.8–7.8 mg/100 ml). The other child had normal serum calcium and phosphate values before and during treatment. Alkaline phosphatase was slightly raised before therapy. In both children alkaline phosphatase fell to between half and one-third of the earlier value during treatment with ACTH. Both children also had generalised aminoaciduria. Because of these abnormal findings x-rays were taken and these showed pronounced osteoporosis.

Electrolyte disturbances and renal failure. Three children had hypokalaemic metabolic alkalosis (serum potassium 2.5–2.6 mmol/l and base excess +10.9–+11.0) during treatment. 10 children had pronounced disturbances of electrolytes at the end of the ACTH treatment or for a few days after it; these disturbances were often combined with marked changes in weight (up to $\pm 11\%$). Four children had oliguria (Figs 1–4). In one of these four a kidney biopsy was made and this showed tubular necrosis.

Case 2

The early history of the child was uneventful. The birthweight was 3050 g, length 49 cm, and Apgar score 9. Development was normal until age 13 months, when the syndrome of infantile spasms was diagnosed. Despite extensive investigations the reason for the spasms remained unknown. Carotid angiography showed slight left-sided hypoplasia of the brain. The pathophysiological significance of this remained unknown. It may have been the result of a prenatal disturbance or a malformation. At age 14 months ACTH (40 units daily) was started. The primary effect was good; the spasms disappeared

Conversion SI to traditional units—serum urea nitrogen: 1 mmol/l $\approx$ 0.71 mg/100 ml.

Fig. 1 Case 2, child with oliguria after being treated with ACTH for 6 weeks.

Fig. 2 Case 3, child with oliguria after being treated with ACTH for 6 weeks.

Fig. 3 Case 4, child with oliguria after being treated with ACTH for 6 weeks.

Fig. 4. Case 5, child with oliguria after being treated with ACTH for 6 weeks.

during the first week and the encephalogram showed no hypsarrhythmia after 3 weeks. Before ACTH the urine had been normal but 4 days after treatment began pyuria was found in several samples (also obtained by catheterisation). Serum creatinine and intravenous urogram were normal and cultures showed no infection.

After 5½ weeks of treatment the girl started to vomit, oliguria and hyperkalaemia developed, and serum urea nitrogen levels rose to 54 mmol/l (75 mg/100 ml), normal levels 4–14 mmol/l (6–20 mg/100 ml). Pyuria was now constantly present and haematuria appeared. Renal biopsy, performed 1 day later, showed slight tubular necrosis. Treatment

included limitation of water intake, anion exchange resin because of hyperkalaemia, and mannitol to enhance urine flow. The function of the kidneys became normal. Blood urea and creatinine levels and creatinine clearance were normal 10 days later. Intravenous urography, 3 years later, was normal.

Case 3

Neonatal hypoglycaemia was the presumed cause of this child's spasms, which appeared at age 6 months. Before the spasms the boy's development had been normal. Initially ACTH had a good effect, but after 5 weeks he started to vomit and lost 7.5% of his weight. Serum potassium rose to 6.1 mmol/l. 10 days after the treatment with ACTH was stopped urine volumes were noticed to be small; however, there was no uraemia. The urine volumes remained small for 8 days, but gradually they became normal.

Case 4

In one child with neonatal hypoglycaemia and neonatal intracranial haemorrhage the diagnosis of infantile spasms was made at age 9 months. The boy had been slightly retarded since birth. ACTH 40 units per day had a good primary effect. Three days after the end of a 6-week course of treatment the urine volumes were noticed to be small and serum potassium was 6.0 mmol/l. Urine volumes remained small for 17 days, but the output returned to normal without any treatment. No uraemia developed.

Case 5

The early history of this child was normal until age 5 months. She then had a febrile gastroenteritis. Soon afterwards she developed infantile spasms. ACTH (50 units a day) had a good effect and was given for 6 weeks. Four days after the end of this period the potassium was at the upper limit (5.0 mmol/l) and small urine volumes were noticed for a week, the weight gain being 600 g or 8% at this time.

Other side effects. Plasma cortisol levels are available as single determinations only in 4 children. During reduction of ACTH dose, 2 days before stopping it, two children had abnormally low values: 0.17 and 0.24 $\mu\text{mol/l}$ (6.0–8.4 $\mu\text{g}/100\text{ ml}$), normal 0.27–0.69 $\mu\text{mol/l}$ (9.7–24.7 $\mu\text{g}/100\text{ ml}$). The third child had no measurable cortisol. This was examined 8 weeks after treatment with ACTH and dexamethasone combined. The fourth child had a normal cortisol level. Side effects in the 2nd and 3rd weeks of treatment were irritability, sleeplessness, and increased spasticity or apathy. The neurological symptoms seemed to increase. These central effects were severe in 14 cases. One child was suspected to have increased intracranial pressure at the time

ACTH was reduced. He was irritable and had long spells of apnoea. Treatment had to be stopped. Another child developed hydrocephalus with increased intracranial pressure during 2½ weeks of therapy with ACTH, and a shunt was installed. It remains uncertain whether ACTH played any part in the raised intracranial pressure. Four children had transient glucosuria during ACTH. Amino-acid analysis was done from the urine of 25, and from the plasma of 4 children. 12 of them had a general renal aminoaciduria during ACTH and 2 also had pronounced changes in plasma amino-acids during ACTH. In one child the thrombocyte count rose to $1000 \times 10^9/\text{l}$. The growth of the children was not studied, as many of the underlying diseases were severe and might have affected growth.

Discussion

ACTH stimulates the secretion of adrenocortical hormones: cortisol, corticosterone, weak androgens and, initially, also aldosterone. Prolonged administration of large doses of ACTH induces hyperplasia and hypertrophy of adrenal cortex (Table 1). Most therapeutic effects of ACTH are probably mediated by glucocorticoids. But ACTH also has direct, less well understood, effects on various organs, including the central nervous system.^{19–24}

Glucocorticoids suppress each stage of the immune response. Not only are bacterial infections enhanced by ACTH treatment, but also viral ones. Latent cytomegalovirus infections may flare up¹⁷ or take an unusual course. *P. carinii* may be a cause of severe lung infections, as in our 2 patients. Other infections—such as measles and varicella which are known to cause severe disease during immunosuppression—may also become dangerous during treatment with ACTH. In this series we especially tried to exclude infections before starting treatment and to avoid them during it. During ACTH therapy it is more difficult to diagnose an infection, because analysis of the blood is affected by cortisol giving rise to leucocytosis and neutrophilia. Despite our efforts even severe infections were not avoided.

The host response and immunological function are altered in relation to glucocorticoid dosage. In our series the risk of infections seems to have been greater when larger doses of ACTH were used. Synthetic analogues seem to carry a greater risk of infections than natural ACTH.¹⁶ This appeared to be so in our series too.

The incidence of osteoporosis is lower with ACTH than with glucocorticoids. In our series only 2 cases were found, but no systematic search was made. Cret *et al.*²⁵ described 5 children with infantile

spasms who developed osteoporosis, hypocalcaemia, hypophosphataemia, and low alkaline phosphatase in blood during Zn tetracosactrin.

One child also had hypomagnesaemia. Glucocorticoids inhibit intestinal calcium absorption. The resultant hyperparathyroidism may be of major importance in the pathogenesis of osteopenia.²⁶⁻²⁷ Furthermore, serum 1-25-dihydroxyvitamin-D₃ is reduced in children receiving glucocorticoids.²⁸

Excessive doses of ACTH (100-180 units) increase the 24-hour urinary-free cortisol to about 20- or 30-fold.²⁹⁻³⁰ The mineralocorticoid effects of cortisol, corticosterone, and desoxycorticosterone presumably play a significant role in the production of undesirable effects of ACTH treatment—such as hypertension, and sodium and fluid retention.

Of the 11 children who were observed to have hypertension 8 had received Zn tetracosactrin, generally in doses of 80 units. This synthetic hormone seems to carry a considerable risk of hypertension, but whether this risk is smaller with corticotrophin remains unknown.

In our hospitals blood pressure is not routinely measured in infants and perhaps a higher proportion of the children had arterial hypertension than is reported. The intracerebral haemorrhage found in 2 cases at necropsy may have been due to hypertension. Taeusch *et al.*³¹ reported intraventricular haemorrhage in 6 out of 7 infants with respiratory distress treated with glucocorticoids. The mechanism by which steroid treatment could lead to intracerebral haemorrhage remains unknown. Blood pressure was measured neither in these cases nor in our fatal cases.

Plasma cortisol levels reach a maximum after 10 days of ACTH administration.¹⁴ In our series hypokalaemia, alkalosis, and hypertension were found during the 2nd and 3rd weeks of such treatment. This often coincided with an increase in the neurological symptoms. It has been suggested that this is due to cerebral oedema resulting from retention of salt and water, or to hypertensive encephalopathy.³²⁻³³ Now it is known that cortisol and ACTH have direct effects on the brain^{19 34-37} and that chronic administration of cortisol increases brain excitability although the concentration of sodium and potassium in the spinal fluid and the brain remains normal.³⁸⁻³⁹

During ACTH treatment the greatly increased mineralocorticoid activity will presumably suppress the renin-angiotensin-aldosterone axis. After withdrawal of ACTH the secretion of cortisol, corticosterone, and desoxycorticosterone will decrease precipitously while the renin-angiotensin-aldosterone axis needs time to recover. A sudden mineralocorticoid and glucocorticoid deficiency will thus ensue. The mineralocorticoid deficiency will tend to lead to a hypo-osmolar contraction of the extra-

cellular volume, and may result in renal failure. The glucocorticoid deficiency adds to the picture of an impaired water excretion capacity. This complexity of disturbance in fluid regulation may explain why losses and gains in weight were observed (Figs 1-4). These withdrawal symptoms had not been reported previously. It is important to know whether the child enters a negative or positive water balance and whether he needs water restriction and diuretics, or more fluids. Glucocorticoid substitution may be necessary after ACTH treatment. We are now trying to analyse the mechanisms of disturbance.

In this series, large doses of ACTH (usually 120 units) gave more side effects than smaller doses (40 units), but the difference was not statistically significant. Infections were however, significantly increased with large doses ($P < 0.05$, $\chi^2 = 4.474$). During treatment with ACTH and dexamethasone combined there were fewer side effects than with other treatment schedules ($P < 0.05$, $\chi^2 = 4.556$). The children in this group were not treated as inpatients during the whole time and side effects were not so carefully recorded. It is therefore difficult to compare them with the others.

When synthetic analogues of ACTH were used 16 (69.6%) out of 23 children had side effects. Eight had hypertension, 3 electrolyte imbalances, and 10 infections. Three of these side effects were severe: long-lasting, severe gastroenteritis in one, and two fatal cases of sepsis. There were considerably more side effects in this group. ACTH produces less impairment of HPA function and growth in children than glucocorticoids. This advantage may be lost if a preparation with too-prolonged an action is used—such as Zn tetracosactrin.²⁹

We believe that ACTH (or perhaps in future its fragments with fewer side effects),¹⁴ alone or combined with glucocorticoids, will maintain its position as the primary drug for the treatment of children with infantile spasms. However, as such treatment has pronounced side effects, a careful watch is essential especially by measuring the blood pressure, examining electrolyte levels, and trying to detect and treat infections early. The appearance of osteoporosis, hypertension, hypokalaemic alkalosis, or exaggerated neurological symptoms should lead to reduction of the dose. If hypertension and salt retention cannot be controlled by salt restriction, dose reduction, or antihypertensive drugs, it is better to change to synthetic glucocorticoids (methylprednisone) which have a less sodium-retaining effect. Often diuretics are given to children with fluid retention during treatment with ACTH. As they increase the potassium loss they are recommended only with regular potassium determinations and perhaps with supplementary potassium.

As side effects, especially infections, seemed to be dose-dependent, the dose should be the lowest that will control the symptoms. The benefit of very high dosages should be reconsidered. Our mode of treatment is based on the clinical experience of Hagberg^{5, 49} and Gamstorp⁴¹ in Sweden who both consider large doses of ACTH important. In other countries considerably smaller ACTH doses are used. Thorough investigations concerning the optimal dosage of ACTH have not been reported. The use of Zn tetracosactrin is not recommended; it has more side effects and can have a fatal outcome. The use of anticonvulsant drugs—such as nitrazepam—as primary treatment should be considered, particularly for instance, if the benefit from ACTH is questionable, as in the case of an already severely damaged child. Furthermore, if the child is known to have a cytomegalovirus infection treatment with ACTH should be avoided.¹⁷ In future, it will probably be possible to test every child for latent cytomegalovirus infection by a rapid method—for example, by fluorescent antibody test. We think it is important to look for other patients in whom treatment with ACTH would be unsuitable.

More knowledge should be gained of the clinical and biochemical actions of ACTH and glucocorticoids in the treatment of infantile spasms. The drugs are used in excessive dosage and for a long time during a period of very active development of the brain—for example, myelination has its maximum at the time that infantile spasms usually begin.

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