POST-VACCINAL ENCEPHALOMYELITIS

REPORT OF TWO CASES TREATED WITH CORTISONE AND ACTH

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Post-vaccinal encephalomyelitis is one of those diseases with a widely varying incidence in different countries.[1] During a recent large-scale vaccination campaign in Cape Town 2 cases came under our care. Since the condition has not previously been reported as having occurred in South Africa, and since the treatment with ACTH and cortisone is still in the early stages of clinical trial, we report these cases and discuss their treatment. The clinical diagnosis of post-vaccinal encephalomyelitis is as yet a presumptive one, and it is with this reservation that the cases are reported under that title.

CASE 1

Mr. E.B., a 47-year-old Norwegian, was admitted to the City Hospital at 6.30 p.m. on 22 December 1955. Fourteen days before this he had undergone a successful vaccination (vesiculation had occurred). He had previously been vaccinated as a small boy in Norway. Two days before admission there was a sudden onset of chills, fever and a frontal headache—the latter two symptoms being progressive till admission. A few hours after the onset of his symptoms he began to vomit and this persisted till the morning of the day of admission. One day before admission his legs became weak, he noted paraesthesiae across his abdomen, and he developed urinary retention necessitating catheterization. He noticed diplopia on the morning of admission. A review of the other systems was non-contributory. Seven years previously primary myxoedema had been diagnosed in him and he was on a maintenance dose of thyroid extract (3 gr. per day), which had kept him symptom-free.

Physical examination revealed a drowsy well-developed man in some distress from headache. The scab from his vaccination was present on the upper part of the outer aspect of the right arm. There was no lymph-node enlargement or tenderness. The oral temperature was 103°F, the pulse rate was 76 per minute (sinus rhythm), the blood pressure 130/80 mm. Hg, and the respiratory rate 26 per minute.

On neurological examination neck stiffness was found to be present. The pupils were equal and reacted briskly to light and on accommodation. The fundi were normal. There was paresis of the right 6th nerve but the other cranial nerves were normal. He was unable to sit up without using his arms. There was marked weakness and moderate hypotonia of both legs (the right more than the left). The finger-nose test was accurately performed and there was no dysdiadokokinesis. The heel-knee test was very poorly performed. Light touch was felt as paraesthesia over thoracic segments 8 to 10. There was gross depression of all modalities of sensation below T10. The biceps, triceps and periosteo-radial reflexes were normal and equal. The right knee-jerk was brisker than the left but the ankle jerks were equal. The abdominal and cremasteric reflexes were absent and Babinski's sign was present bilaterally. The rest of the physical examination was normal.

After admission the patient was catheterized owing to inability to void (hypogastric discomfort was present). The urine was normal. The sedimentation rate was 14 mm. in the 1st hour by Westergren's method, the haemoglobin 15 g.% and the VPC 48%. The white blood-cell count was 8,800/per c.mm., and the smear showed 72% polymorphs, 22% lymphocytes, 4% monocytes, 1% eosinophils and 1% basophils. The red cells looked normal and adequate numbers of platelets were seen.

Lumbar puncture produced clear cerebrospinal fluid containing 12 polymorphs and 44 lymphocytes per c.mm. The protein was 60 mg.%, the chlorides 700 mg.% and the glucose normal. No organisms were found with Gram and Ziehl-Neelsen stains or on culture. The blood and C.S.F. Wassermann reactions were negative.

Within 2 hours of admission the following scheme of treatment was started. Oral cortisone was given for 4 days—100 mg. *tds* on the 1st day, 50 mg. *tds* on the 2nd, 25 mg. *tds* on the 3rd, and 25 mg. *bd* on the 4th. ACTH was given for 8 days by intramuscular injection, starting on the 3rd day. 40 u. were given on each of the 3rd and 4th days, 20 u. on each of the 5th to 7th days, 10 u. on the 8th and 9th days and 5 u. on the 10th day. His maintenance dose of thyroid extract was given from 2 days after admission. He received no other drugs at all. His temperature declined rapidly, reaching 98·4°F 36 hours after admission. Thereafter it rose again slightly and fluctuated below 100°F for 5 further days (the catheter was in during this period). The encephalitic symptoms improved rapidly and 24 hours after admission he was quite alert, the headache was only slight and the diplopia and right 6th nerve paresis had disappeared.

The myelitic symptoms and signs improved more slowly. Two days after admission he was able to sit with ease, the knee jerks were equal and the cremasteric and abdominal reflexes

were present. An indwelling catheter which had been inserted on the day after admission was removed on the 6th day and he had no further urinary difficulty. By this time significant objective sensory disturbance was no longer present but paraesthesiae in the legs and eventually only in the feet persisted till 16 days after admission. The left plantar reflex became flexor 5 days after admission and the right plantar 12 days after admission.

The patient was discharged 21 days after admission without any neurologic symptoms or signs.

CASE 2

H.C., a 10-year-old European female, was admitted to the City Hospital on the evening of 27 December 1955. Fifteen days before admission she had been vaccinated successfully for the first time. One day before admission she complained of headache, became feverish, and was unusually quiet. From the morning of the day of admission she had lain curled up in bed as if asleep. No convulsions had occurred.

Physical examination showed a stuporose child lying curled up in bed. Vaccination scars were present on the upper part of her left arm and the regional lymph-nodes were enlarged. The oral temperature was 101·8°F, the pulse rate 100 per minute, the respiratory rate 24 per minute, and the blood pressure 125/70 mm. Hg.

Neurological examination revealed neck stiffness and the presence of Kernig's and Brudzinski's signs. The pupils were equal and reacted briskly and the rest of the cranial nerves as far as could be tested showed no abnormality. There were no motor abnormalities, the deep reflexes were all present and equal and the plantar reflexes were flexor. The rest of the physical examination was negative. The white blood-cell count was 20,000 per c.mm. Lumbar puncture produced a hazy fluid containing 30 polymorphs and 120 lymphocytes per c.mm. The protein was 40 mg.% and the chlorides 695 mg.%, the glucose was normal, and there were no organisms to be found.

On the morning after admission her temperature was 99·8°F and her level of consciousness had improved to the extent that she was now confused and restless. At this time cortisone administration was started and it and ACTH were given according to the scheme outlined in the previous case. On the morning of the 2nd day after admission her temperature was normal and remained so, and her level of consciousness had improved to the extent that she could answer questions with 'yes' or 'no'. Thereafter improvement was rapid; her mental state was quite normal and there were no abnormal signs 3 days after admission. She was discharged completely well and with no abnormal neurological signs 21 days after admission.

DISCUSSION

The incidence of encephalomyelitis in reported series has been:[1] Holland 1 : 4,656 vaccinations (186 cases between 1924 and 1931), Sweden 1 : 20,000 (38 cases between 1924 and 1933), England 1 : 33,000 (175 cases between 1922 and 1929),[2] Germany 1 : 100,000 (134 cases between 1927 and 1933), United States 1 : 110,000 (45 cases in 1947).[3] It has not been reported from Soviet Russia or Spain. Most of the cases occurred after primary vaccination and as a sequel to revaccination it is very rare—not more than 1 : 50,000 vaccinations in Dutch experience and about 1 : 800,000 in Germany—hence the especial interest of case 1. The increased incidence in Holland appears not to depend on the type of serum used there, since there was no decline in incidence when Spanish serum was used.

The disease is practically unknown in infants vaccinated under the age of 1 year, the bulk of cases occurring with primary vaccination of children between the ages of 3 and 13 years.[4] The limits of the period between primary vaccination and nervous disease have extended from 5 to 23 days;[5] in 4/5ths of cases it ranges between 9 and 13 days, with a predilection for the 11th or 12th day after vaccination. After revaccination the period is shortened as a rule even to 2 or 3 days.[6]

Clinical Course. In most cases the onset is sudden and progress rapid. The disease starts with headache, drowsiness, vomiting and fever. In children fits are common. Ocular palsies, inequality of pupils, and disturbed pupillary reactions, may occur. The ocular fundi are usually normal but transient papilloedema has been observed. Flaccid or upper-motor-neurone paralysis of some of the limbs often develops and is associated with absent deep and extensor plantar reflexes. Disturbance of the rectal and urinary-bladder sphincters is frequent. Neck rigidity was noted in half of van Hunsel's 108 cases.[7] Transverse myelitis may be unaccompanied by encephalitis. Rare symptoms which have been described are choreic or athetotic movements, tremor, dysarthria, dysphasia, ataxia, hiccup, neurotic symptoms, hyperidrosis and salivation.

As a rule the cerebrospinal fluid either is normal or shows a moderate lymphocytosis (up to 400 per c.mm.[3]) with excess of protein.

Acute phases seldom last longer than a week and are often briefer; in those who survive, complete recovery within a space of perhaps another week is the rule, though it may be delayed for months. The mortality rate is high. It has oscillated in Holland between 25 and 59% with an average of 31%. In England it averages about 30%.[8] Greenberg and Appelbaum[3] reported a mortality of 4 among 45 cases. Death is usually due to exhaustion, coma, respiratory paralysis, or bronchopneumonia. If recovery occurs it is usually remarkably complete and residual symptoms are exceptional.

Pathology.[9] Naked-eye changes consist of congestion and oedema of the nervous system. Microscopically there is marked perivascular infiltration of mononuclear cells. The most characteristic feature of the inflammation is the occurrence in the white matter of zones of demyelination around the vessels, especially the veins. Necrosis of nerve cells and neuronophagia is not seen. The most intense changes are encountered in the lumbar and upper sacral regions of the spinal cord and in the pons. In the mid-brain, the substantia nigra is the structure most affected. Inflammatory changes may be present throughout the whole length of the nervous system.

Treatment. The high mortality rate of the disease (30-50% in most series) and the lack of a proven therapeutic agent have prompted the trial of new methods of treatment. (Intrathecal or parenteral immune serum has been recommended[10] but there is no definite evidence that it is of value.) Since the disease may spontaneously reverse its course from progression to rapid recovery conclusions cannot be drawn from individual cases but will have to rest on the evidence obtained from controlled trials. At first sight, the problem of whether a given therapeutic method is effective or not should be more readily solved with post-vaccinal encephalitis than with the other post-infective encephalitides because of its greater mortality rate. But the mortality rate varies; in Greenberg and Appelbaum's series,[3] it was as low as 4 of 45 cases, and this possibility of a greatly varying mortality rate

must temper with caution optimistic assessments of the results of clinical trials.

In most studies post-vaccinal encephalomyelitis is considered together with the other acute post-infective encephalomyelitides because of their similar clinical and pathological features, and discussion of the rationale of therapy will be on the basis of post-infective acute encephalomyelitis in general.

Rationale of Therapy. There is at present no final agreement on the pathogenesis of acute post-infective encephalomyelitis,[11] but there is a fair amount of evidence that it may depend to some extent on an allergic mechanism. Miller,[12] in 1951, drew analogies between the neurological syndromes of serum sickness, polyarteritis nodosa and acute disseminated and post-infective encephalomyelitis. In all of these conditions there is a tendency to gross and often evanescent focal symptoms arising at every level of the nervous system, and occasional apoplectic syndromes suggestive of lesions involving the major cerebral blood-vessels. Similar histological changes concentrated in close relation to the cerebral vasculature occur in all the post-infective encephalomyelitides. Also a suitable time-interval appears necessary between the inciting disease or injection and the development of encephalitis (presumably the time necessary for the development of hypersensitivity). On the basis of these observations Miller suggested that some such cases of acute encephalomyelitis might have their foundation in an allergic vasculitis and that the trial of cortisone and ACTH in their treatment might produce favourable results.

A fair amount of indirect experimental evidence can also be cited in favour of the allergic hypothesis. Encephalomyelitis histologically similar to the human form may be induced by single or multiple 'sensitizing' subcutaneous injections of brain, spinal cord or nerve emulsions into rabbits, monkeys, guinea-pigs and other animals.[13] The experimental syndrome may be inhibited by agents known to inhibit the development of hypersensitivity, such as pyromen, salicylates, para-aminobenzoic acid nitrogen mustard, and particularly cortisone and ACTH,[13–17] and is accentuated by the use of the Freund adjuvant.[18]

Results of Therapy. Since Miller's suggestion there have been several reports of the use of ACTH in encephalomyelitis, well summarized by Selling and Meilman.[19–25] Using the criterion that significant objective improvement starting within 24 hours is due to the therapy, [20,19] 14 episodes out of 19 (occurring in 11 out of 16 patients) were considered to have been favourably influenced. In 3 of the other 5 cases improvement started between 48 and 72 hours after the start of therapy, in one (the only case of the 16 who had no prodrome or preceding injection) the illness was quite unaffected and resulted in severe neurologic signs, and in the other (a case of post-measles encephalomyelitis) death occurred on the 2nd day of treatment. The relapses associated with reduction of dosage noted in Miller's first case[20] and in Selling and Meilman's case,[19] and the resumption of improvement when the dosage was increased, render coincidence a not entirely satisfactory explanation for the results observed.

We have found only 2 reports of ACTH therapy in post-vaccinal encephalomyelitis. Ligterink[24] reported 2 cases in which he considered benefit to have been obtained, and a few cases were reported in the *U.S. Armed Forces Medical Journal*[25] to have benefited.

Both of our cases exhibited significant objective improvement within 24 hours of starting therapy, but in Case 2 some improvement had already occurred before treatment was started. Nevertheless, as Ligterink[24] pointed out, proper evaluation of the usefulness of this type of therapy will have to await reports based on controlled trials and these are awaited with interest.

The clinical usefulness of this type of therapy will need to be solidly founded since these drugs are not without their dangers. Aside from their generally potentially harmful effects, their use without appropriate chemotherapy in bacterial (and probably virus) infections of the nervous system might be disastrous.

SUMMARY

Two cases of post-vaccinal encephalomyelitis treated with cortisone and ACTH are described. The rationale of this treatment and its clinical applications are discussed.

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