

A NEUROLOGICAL SYNDROME IN INFANTS RECOVERING FROM MALNUTRITION

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During the past two years, eight infants admitted to this hospital developed neurological disturbances while recovering from malnutrition. These disturbances cleared up partially or completely within several weeks or months of appearance. Summaries of the history and examination of each of the eight infants are given in the accompanying table, but certain aspects of the syndrome are described in greater detail below.

Before the onset of neurological complications these infants were not distinguishable from other

severe cases of infantile malnutrition, of which about 500 pass through our wards every year.

The syndrome appeared not while the children were severely ill with malnutrition but some one to eight weeks after dietetic treatment had been instituted and when there was clear evidence of convalescence.

Coarse tremors, Parkinsonian in type, were the earliest and most constant abnormality. They were always fully developed within two to four days of onset. Once they were established, they ceased only

TAB
ANALYSIS OF CAS

	Case 1	Case 2	Case 3	Case 4
Race (tribe)	Eurafrican	Swazi	Zulu	Zulu
Sex †	Male	Male	Male	Male
Age (in months)	13	14	12	12
Month of admission	January	June	February	July
Weight on admission	11½ lb.	15 lb.	13 lb.	9½ lb.
Manifestations of malnutrition on admission	Atrophic hair, generalized wasting, gross rickets	Atrophic and depigmented hair, oedema, cheilosis, pellagrous dermatosis	Gross rickets, atrophic and depigmented hair	Atrophic and depigmented hair, angular stomatitis, glossitis, pellagrous dermatosis
Duration of diarrhoea before admission	Six weeks	Four weeks	Two weeks	?
Feeds before admission	Proprietary infants' cereal. Occasionally ¼ pint of milk with the cereal preparation, but usually no milk. Sometimes mashed potatoes	Maize porridge without milk three times a day, no milk, or other food containing animal protein, for past 5 months	Soured maize porridge and sugar, no milk	Condensed milk, highly diluted; also oat meal and barley gruels without addition of milk
Treatment of malnutrition	Altmann formula*	Altmann formula*	Skimmed milk mixture	Altmann formula*
Additional vitamins	Nil	Vitamin B Co., 0.5 ml., on day after admission	Nil	Riboflavin, 5 mg. t.i.d., from 5th day after admission
Interval between change of diet and onset of tremors	27 days	12 days	8 weeks	7 days
Parts affected by tremors	Right arm and leg, tongue and lower jaw	Both arms and right leg	Extremities, head, jaw and tongue	Extremities, head, jaw, tongue and eyelids
Myoclonus	Nil	Both arms and right leg	Extremities	Arms and jaw
Opisthotonus	Present	Nil	Nil	Present
Tendon reflexes	Exaggerated	Exaggerated	Exaggerated	Exaggerated

* Two ounces of dried skimmed milk, 1 oz. of dextrin-maltose and one drachm of lactic acid B.P. are dissolved in one pint of water 25 mg. of ascorbic acid which is added to one of the daily feeds, no vitamins, liver extracts or drugs are used in this method of treatment.

during sleep. They involved most commonly and most severely the hands, although one hand was usually affected to a greater extent than the other. All infants except one (No. 8) showed tremors of the lower extremities, but in four cases (Nos. 1, 2, 5 and 6) only one of the legs was involved. In four patients (Nos. 1, 3, 4 and 5) tremors were seen to affect the head, the lower jaw and the tongue in addition to the extremities, and there was also sagging of the jaw and a vacant facial expression. However, neither in these nor in the remaining infants was there any evidence of excessive salivation.

Cogwheel rigidity was always present in extremities showing tremors, but lead pipe rigidity could not always be demonstrated in limbs not affected by tremors.

All of the patients showed disturbances of posture. These manifested themselves usually only in the hands, which were held in a half-closed position, deviated at the wrist towards the ulnar side and with the thumb adducted into the palm (Fig. 1). Only if the tremors were severe were the arms flexed at the elbows. Two patients (Nos. 1 and 4) suffered from opisthotonus for several days after the onset of tremors,

and this was associated with marked neck rigidity.

While tremors, cogwheel rigidity and postural abnormalities indicated the existence of an extrapyramidal disorder, there was also evidence of an involvement of other parts of the nervous system. All infants showed grossly exaggerated tendon reflexes, though clonus could never be demonstrated.

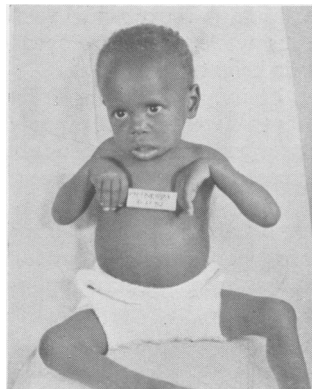


FIG. 1.—Case 6 shortly after admission, showing sagging of jaw and the typical posture of upper extremities.

Four patients (Nos. 3, 4, 5 and 7) suffered from myoclonus in the limbs most severely affected by tremors. This occurred usually at the rate of one per second and resulted in a flexion movement of the arm at the elbow or the leg at the knee or hip. Case 5, in which myoclonus was more widespread than in any of the others, will be

OF PRESENT SERIES

Case 5	Case 6	Case 7	Case 8
Xosa	Msutu	Zulu	Zulu
Male	Male	Male	Male
16	22	10	15
August	November	February	March
14 lb.	17 lb.	14½ lb.	13½ lb.
Atrophic and depigmented hair, generalized oedema, pellagrous dermatosis, angular stomatitis, glossitis	Sparse, atrophic, black hair, shiny, atrophic skin, oedema of legs	Mild pellagrous dermatosis, sparse, atrophic and depigmented hair, generalized depigmentation of skin	Atrophic black hair, angular stomatitis, some hyperkeratosis of the skin developed in hospital
No diarrhoea according to mother, but diarrhoea on admission	3 weeks	1 week	4 weeks
Proprietary infants' cereal containing 20% of dried skimmed milk	Maize gruel made with water, probably no milk	Proprietary infants' cereal, greatly diluted with water, no milk	Haphazard feeding, proprietary infants' cereal. Total quantity of milk about 12 oz. per day
Altmann formula*	Normal diet for age	Altmann formula*	Altmann formula*
Nil	Nil	Nil	Nil
12 days	14 days	13 days	27 days
Arms, left foot, jaw and tongue	Arms and right leg	Extremities	Arms only
Left arm and leg, tongue, respiratory and frontalis muscles	Nil	Nil	Nil
Nil	Nil	Nil	Nil
Exaggerated	Exaggerated	Exaggerated	Exaggerated

This mixture is given to malnourished infants in amounts of 2½ oz. per lb. body weight per day, divided into six or more feeds. Except for (Altmann, 1948).

described in greater detail later. The tremors disappeared during sleep, but the jerks caused by the myoclonus could be detected frequently while the child was sleeping soundly. All children with myoclonus sweated profusely.

With the exception of Cases 1, 7 and 8, the infants were unable to carry out voluntary movements with those limbs which were trembling most severely. In Cases 2, 4 and 5 voluntary movements were confined to head and eyes while the neurological complications were at their height.

Irritability is a feature of infants suffering from malnutrition, and all eight cases were irritable before the tremors started. However, there was no doubt that the irritability increased when the tremors began.

One case (No. 5) was confused for 24 hours during an attack of aspiration bronchopneumonia, but this was doubtless due to cerebral anoxia, because none of the other children showed any clouding of consciousness, and this particular child improved rapidly when the air-way was cleared and oxygen was administered. These children were usually more wakeful than others of their age, and two cases (Nos. 2 and 5) suffered from severe insomnia and were hardly ever seen asleep until sedated with 3 grains of phenobarbitone per day.

Further Course of the Neurological Disorder

In Case 1 death occurred before there was any change in the nervous manifestations, and was due to gastro-enteritis. The other patients improved gradually. If myoclonus or opisthotonus were present, these were the first to disappear, and they did so always within one or two weeks of onset. The tremors left the legs several weeks before a similar improvement was noticed in the upper extremities. Tremors could sometimes be felt in the fingers for some weeks after all visible evidence had gone. Voluntary movements returned before tremors had ceased. In the case of the hands, they appeared first in the thumb and index finger, and the children were seen to play with these fingers while the others were still flexed inactively into the palm.

The neurological disturbances did not relapse, once they had begun to regress. In Cases 2, 7 and 8 the patients left hospital without any abnormal neurological signs, except brisk reflexes. In Case 4 there were still tremors and rigidity of the left arm and a tremor of the tongue when the child was discharged from hospital four months after the start of the syndrome. Unfortunately, he failed to attend the out-patient department after discharge.

However, when he was re-admitted to hospital six months later with bronchopneumonia, examination of the nervous system was normal except for abnormally brisk reflexes. One child (Case 6) is still under observation as an out-patient, some eight months after the start of tremors. He still has a Parkinsonian facies (Fig. 2), his gait is shuffling, his left arm shows lead pipe rigidity and his tendon reflexes are abnormally brisk. However, he no longer suffers from tremors and he is normal mentally. Two other patients (Nos. 3 and 5) had remains of tremors and cogwheel rigidity on discharge from hospital. Their further progress could not be observed because the parents did not bring them to the out-patient department, and they could not be traced at their former addresses. Thus, apart from the one patient who died, all infants recovered almost completely from the syndrome.

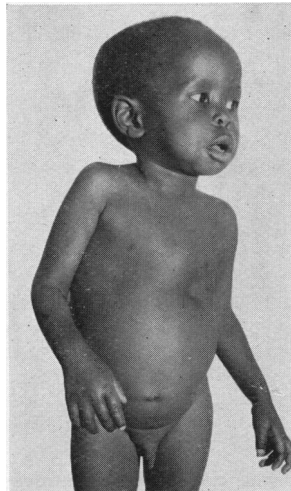


FIG. 2.—Case 6 seen 8 months later. His jaw is still sagging, but his posture is almost normal. The Harrison's sulcus was present on admission, but there was no evidence of active rickets.

Results of Investigations

Serological tests for syphilis were negative. Mantoux tests in strengths of 1 in 1,000 and 1 in 100 were also negative. Two children had clinical evidence of rickets and the bones showed evidence of it on x-ray examination. Although all eight infants were suffering from diarrhoea before the onset of tremors, pathogenic bacteria were demonstrated only in the stools of Case 8, which yielded a growth of *S. flexner*. The serum in Case 3 agglutinated *S. flexner* in a significant titre of 1 in 256. Diarrhoeal stools are almost the rule in cases of infantile malnutrition in this country, but pathogenic bacteria are not responsible for these (Kahn and Robertson, 1952). It is, therefore, assumed that the diarrhoea in the remaining six infants was not attributable to intestinal infection with bacteria, but that it was caused by the underlying nutritional disorder.

In malnourished infants seen at this hospital the liver function tests are usually abnormal, and they

remain so for some time during convalescence. In several of the cases liver function tests were markedly abnormal. However, in Case 8 the thymol flocculation and turbidity, Takata-Ara and colloidal red tests were normal when tremors began, although mild liver dysfunction was suggested by an albumin/globulin ratio of 3.4:3.3. Needle biopsies of the liver were carried out on Cases 4 and 5. No structural abnormalities could be detected in these specimens, apart from mild fatty changes.

The urine of three of the infants (Nos. 4, 5 and 6) was examined by paper chromatography for abnormal excretion of amino-acids. No such abnormalities were detected.

Only in Case 3 did lumbar puncture show any abnormal findings. On the fourth day after the onset of tremors the cerebrospinal fluid contained 18 polymorphonuclear leucocytes and 8 lymphocytes per c.mm., with total protein 76 mg. per 100 ml., glucose 63 mg. per 100 ml., and chlorides 721 mg. per 100 ml. Six days later the cerebrospinal fluid did not contain any cells and the protein content was 46 mg. per 100 ml.

Electro-encephalograms were carried out on Cases 4, 5 and 6. They show scattered areas of abnormal electrical activity, but discharge phenomena were not seen.

Post-mortem Findings

Only one patient (No. 1) died, death being due to gastro-enteritis of unknown aetiology which was contracted in hospital one month after the onset of tremors. Post-mortem examination was carried out 48 hours after death. Unfortunately, the significance of the case was not realized at the time and only a few parts of the brain were taken for microscopic examination. They were reported on as follows:

'Section of the meninges over the region of the central sulcus shows slight oedema. The underlying brain is congested and there is well marked interstitial and perivascular oedema. Around an occasional vessel there is recent extravasation of blood cells into the perivascular spaces. Similar, less marked, changes are noted in the cortex from the region of the Sylvian fissure.

The basal ganglia and the internal capsule show congestion and interstitial and perivascular oedema. The nerve cells show post-mortem autolysis, but no other definite degenerative lesions. Sections from the mid-brain and medulla, including the olive, show no significant pathological lesions, apart from congestion and interstitial and perivascular oedema.'

The cerebral sinuses did not reveal any signs of thrombosis. The lungs showed evidence of terminal

bronchopneumonia, and there were mild fatty changes in the liver. No other abnormalities were detected.

(In the assessment of the post-mortem findings of the brain it should be kept in mind that any or all of the abnormalities described may have been caused by the fatal attack of gastro-enteritis.)

Detailed Case Reports

The case reports of No. 5 and No. 7 are presented in greater detail, the first as an example of a severe and the second as an example of a mild variant of the condition.

Case 5. A boy (Xosa), aged 16 months, was admitted to hospital on August 16, 1952, with the diagnosis of 'nutritional oedema'. The child weighed only 14 lb. There was generalized pitting oedema. Other evidence of malnutrition was provided by severe pellagrous dermatosis, depigmentation of hair and skin, glossitis and angular stomatitis.

The mother stated that the child had been fed artificially since birth. For 10 months before admission feeds had been prepared from a proprietary infant food which consists of maize (50%), dried skimmed milk (20%) and a mixture of cereals other than maize (30%). This had been mixed haphazardly with water, instead of milk, and had been administered to the infant whenever he cried.

In hospital the child received the standard Altmann formula without additional vitamins. For the period August 18-22, he was kept on a metabolic bed for balance studies, and an accurate note was taken of his clinical condition. It is certain that during this time there were no unusual nervous manifestations, apart from the irritability which is commonly associated with infantile malnutrition. On August 26 and 27, the patient's condition was greatly improved, his irritability had lessened, and he had begun to play with his toys. On August 28, 12 days after admission to hospital, severe tremors were noticed in the left arm. However, the child was still using both his hands while playing. On the following day the tremors were also noted in the left foot and the right arm, and these limbs showed cogwheel rigidity. The condition remained unchanged the following day, but on August 30 profound deterioration had set in. All four extremities were affected by tremors and cogwheel rigidity. Voluntary movements, except those of the eyes and the head, had ceased. Severe myoclonus was producing a one per second flexion of the left arm and the left leg. The tongue showed a fine tremor and, in addition, myoclonic jerking at a rate of two per second. Myoclonus was also detectable in the frontalis muscles, the sternomastoids and the respiratory muscles, the latter causing jerkiness of respiration. The child appeared to be unable to swallow, and mucus was collecting in the throat. Examination of the chest indicated the presence of bronchopneumonia. The patient was cyanosed, his consciousness was clouded and he was sweating profusely.

During the following four days the child was fed nasally, mucus was aspirated from the nasopharynx, and the pneumonia was treated with penicillin and oxygen. Under this treatment the cyanosis disappeared, consciousness returned to normal, and the clinical signs of bronchopneumonia cleared up. At this stage it was realized that the patient had hardly ever slept since the onset of the tremors and that he was usually looking around anxiously. He was, therefore, given 3 grains of phenobarbitone per day. Thereafter he slept for longer periods, but did not close his eyes during sleep.

The nervous manifestations showed definite signs of abating nine days after they had begun. The myoclonus disappeared, and the legs were no longer affected by tremors. Seven weeks later the child began to smile and to take notice of his surroundings. A few days after this he was able to sit upright. However, the tongue and the hands were still trembling, the face bore a mask-like expression and the lower jaw was sagging. Twelve days after sitting up the child began to crawl, but was unable to use his left hand in doing so.

The tendon reflexes were abnormally brisk from the day neurological complications had first been seen until the patient left hospital four months later. On discharge the patient's left hand was still affected by tremors and cogwheel rigidity; he was not using his left hand when crawling; his lower jaw was sagging and his tongue was trembling occasionally.

The parents did not attend the out-patient department with the patient after discharge, and attempts to locate the infant at home were unsuccessful.

Case 7. A boy (Zulu), aged 10 months, was admitted to this hospital on February 20, 1953, with the diagnosis of malnutrition and early bronchopneumonia.

The diagnosis of bronchopneumonia was confirmed by x-ray examination and the abnormal chest signs resolved within one week under treatment with penicillin and sulphonamides.

The diagnosis of malnutrition was based on mild pellagrous dermatosis over the forehead and extensor surfaces of the legs, atrophic scalp hair and depigmentation of the parts of the body not affected by the dermatosis. The child was a little underweight at 14½ lb.

He had been under the care of his grandmother for several months. She had fed him on a proprietary infant cereal which does not contain milk. This had been cooked with water, and not with milk as recommended by the manufacturers. The child had not received any milk or other food while living with his grandmother.

In hospital the malnutrition responded readily to the Altmann formula, but 13 days after admission coarse tremors were noticed in the left hand. The following day tremors affected all four extremities, and these were also the seat of cogwheel rigidity and myoclonus. However, no abnormalities were seen elsewhere in the body, the child was only mildly irritable, and he was able to carry out voluntary movements. All tendon reflexes were abnormally brisk and the child was unable to sit up unsupported.

The myoclonus disappeared entirely in four days. Ten days later the tremors had diminished in intensity, except those of the left hand, and the child was able to sit up unsupported. All tremors ceased 20 days after they had first been noticed. The briskness of the reflexes, however, remained unchanged.

Discussion

Severe infantile malnutrition is common in the non-European community of South Africa. It is usually caused by a cereal diet to which little or no milk has been added. The common manifestations of the deficiency state resulting from such a diet have been described in articles dealing with infantile pellagra, malignant malnutrition and kwashiorkor. Advanced cases suffer from retardation of growth, oedema, pellagrous dermatosis, mucosal lesions, atrophy of the scalp hair, depigmentation of the skin and scalp hair, diarrhoea, hypo-albuminaemia and fatty liver. However, neurological disturbances are not a feature of infantile malnutrition in South Africa, with the notable exception of the irritability to which reference was made above.

It might, therefore, be thought that the association of the condition just described with infantile malnutrition was a fortuitous one. This is not likely to be the case, even though its incidence was less than 1% of all cases of malnutrition admitted to hospital, because (1) this syndrome has not been observed among tens of thousands of children who attended this department for conditions other than malnutrition, and (2) the syndrome developed in our cases at a specific time, namely, during convalescence from malnutrition.

We must now explain why the condition has not been noted by others who see large numbers of malnourished infants. Suspicion falls on environmental factors and the dietetic management of infantile malnutrition practised at this hospital.

It is known that extrapyramidal nervous lesions, such as described above, can be caused by carbon monoxide, manganese, nitrous oxide, carbon disulphide, potassium cyanide and barbiturates. None of the eight children were in contact with these substances before the onset of tremors. Contamination of the feeds in hospital can be ruled out, because in Case 3 the tremors developed while the child was under treatment with skimmed milk at home, and in Case 6 symptoms occurred when the patient returned to a better diet at home after boarding in the country with his grandmother who had fed him on cereals until he began to suffer from nutritional oedema.

The eight infants were not suffering from a post-encephalitic syndrome because (1) not one of them

showed abnormal neurological signs before the onset of tremors; (2) they did not show clouding of consciousness either before or after admission to hospital (except Case 5, during anoxia caused by bronchopneumonia); (3) the seven survivors recovered from the syndrome, either completely or partially, in a matter of weeks or months, whereas the neurological damage of encephalitis is usually permanent.

Severe liver disease may be combined with nervous manifestations such as those described above. Hepato-lenticular degeneration is an example of this association, but tremors, cogwheel and lead pipe rigidity and myoclonus occur also in acute and subacute necrosis of the liver (Walshe, 1951). However, the liver in Case 1, where death was due to an intercurrent illness, showed no abnormalities, except mild fatty changes. The same applies to the needle biopsies of the livers of Cases 4 and 5. Furthermore, flocculation tests for liver function carried out in Case 8 were normal when tremors began. We can, therefore, state with some assurance that severe liver damage played no part in the pathogenesis of the syndrome.

Disorders of the extrapyramidal nervous system have been observed in pellagrins (Belmondo, 1889; Lewy, Spies and Aring, 1940). There is no fundamental difference between pellagra and what is commonly called infantile pellagra, malignant malnutrition, kwashiorkor or infantile malnutrition. Both adult and infantile deficiency states are caused by a diet which lacks animal protein and which is composed largely, if not entirely, of food of vegetable origin. In adults the consumption of this diet results in a disease in which signs of vitamin B deficiency predominate. In the quickly growing child signs of protein deficiency are prominent and often overshadow those of vitamin deficiencies.

This multiple deficiency state is treated at this hospital with the Altmann formula. As stated before, vitamins or other additions are not employed. This regimen assures an adequate supply of protein of high quality, but its vitamin content is unknown and may be inadequate under certain circumstances. It is important to recall that the two children who developed tremors before admission to hospital also received a diet with a satisfactory protein content but no additional vitamins.

The repair of the state of malnutrition depends not only on an adequate intake of protein of high quality, but also on the availability of other essential components of the food. If there is a deficiency of the latter, the process of repair may be expected to proceed in a disorderly fashion. It is suggested that the syndrome described above may be a manifestation of such an imbalanced recovery, caused by a diet rich in protein but deficient in other essential factors.

The nature of these missing factors is yet unknown. Lewy *et al.* (1940) state that Bean and Spies obtained some dramatic recoveries from the Parkinsonism of pellagra when patients were treated with vitamin B6 (pyridoxin hydrochloride). This vitamin was given to two of our patients when they were suffering from the neurological complications (Cases 5 and 8). Both these patients improved gradually, but it is doubtful whether improvement was appreciably speeded up by this vitamin.

Summary and Conclusions

Among 1,000 cases of infantile malnutrition admitted to Baragwanath Hospital there were eight with characteristic neurological disturbances. These consisted of tremors, similar to those seen in Parkinsonism, cogwheel rigidity and lead pipe rigidity of the extremities and exaggerated tendon reflexes. Some infants also showed myoclonus, opisthotonus and insomnia. These manifestations developed at a time when there were already signs that the nutritional state of the patients was improving. The syndrome disappeared entirely, or nearly so, within a few weeks or months of onset.

It is suggested, albeit on slender evidence, that the syndrome was the result of an imbalanced therapeutic regimen.

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