HYPERVITAMINOSIS A

BY

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Since Josephs (1944) first described hypervitaminosis A there have been numerous cases reported in the American literature, notably by Toomey and Morissette (1947) and by Caffey (1950 and 1951). No record of such cases has been traced in the British literature and so the occurrence of two examples of this condition is thought to be worthy of record.

Case Reports

Case 1. R.P., a boy of 6 years, was admitted to the Wakefield General Hospital on March 9, 1955. He had had frequency of micturition and nocturnal enuresis for two weeks. This was followed by vomiting and anorexia for one week. Then he developed pain in the arms, legs and forehead of such severity as to prevent him from sleeping. He was thought to have lost weight during the previous three weeks.

Xeroderma had been diagnosed at the age of 5 months and had been treated by ointment until a dermatologist prescribed 'avoleum', a dram b.d. This was continued until six weeks before admission when the dose was increased, probably by the mother, to 'avoleum', drams 2 b.d. It was estimated that the intake of vitamin A over the six weeks before admission was about 463,040 i.u. per day.

On admission the child was ill and fretful with a temperature of 100° F. The skin was salmon pink and scaling. The lips and nasal mucocutaneous junctions were cracked and bleeding, and very sore. The arms and legs were extremely tender to the lightest touch, subcutaneous tissues were swollen, most markedly over the tibiae. The liver and spleen were both enlarged three fingerbreadths below the costal margin. There was a bilateral conjunctivitis.

During the first week in hospital the skin became more scaly and the patient continued to complain of pain in the upper limbs and back which caused difficulty in sitting. Oedema of the face developed on March 13. The temperature dropped to normal by the end of the week.

A radiograph of the chest was normal (March 9).

On March 10 the haemoglobin was 93%, and the total white blood cell count 10,600 per c.mm. (neutrophils 60%, lymphocytes 38%, monocytes 2%). The E.S.R. was 17 mm. in one hour. The Mantoux test (1 : 1,000) was negative.

On March 11 the blood cholesterol level was 316 mg. per 100 ml.

On March 12 albumin – was found in the urine, and also occasional hyaline and granular casts and very occasional pus cells.

On March 15 the cerebrospinal fluid was normal. The blood urea level was 88 mg. per 100 ml.

During the second week the pain in the limbs and back subsided, and by the end of the week a considerable improvement in the skin was noticed, it being quite soft and moist. The dry, cracked lips persisted. On March 18 the prepuce swelled. The spleen was slightly smaller.

A radiograph of the skull and limb bones on March 17 showed normal appearances.

The serum bilirubin level was 0·3 mg. per 100 ml.

A trace of albumin and a few pus cells were found in the urine.

On March 21 a water dilution and concentration test was normal.

Thymol turbidity was 3 units.

The alkaline phosphatase level was 25·2 units per 100 ml.

The blood carotene was 20 μg. per 100 ml. and the blood vitamin A, 450 i.u. per 100 ml. (normal 50-130 i.u. per 100 ml.).

The oedema of the prepuce had cleared by the third week, and, apart from cracked lips (Fig. 1), the boy was

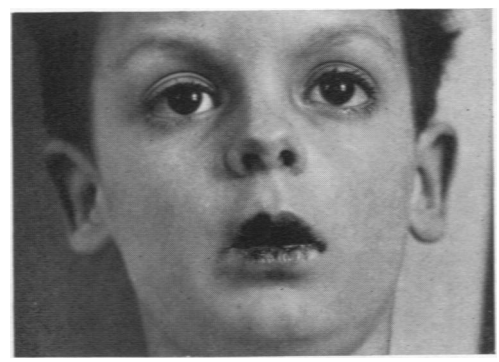

FIG. 1.—Hypervitaminosis A showing cracked and bleeding lips.

free of symptoms. The liver had reduced slightly in size, and the urine was normal. On March 26 the blood urea level was 40 mg. per 100 ml.

At the end of the fifth week the hair was being shed

and the scalp became scaly. The rest of the skin was in good condition.

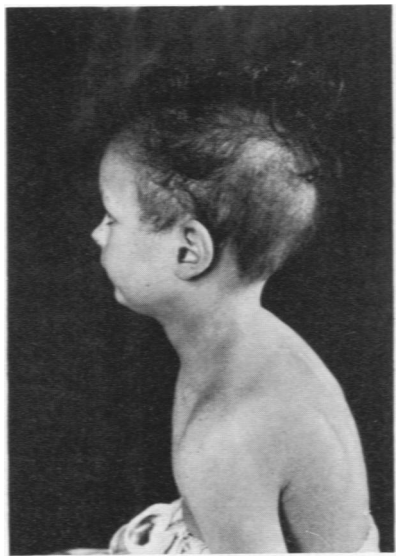

FIG. 2.—Hypervitaminosis A showing loss of hair.

On April 4 the blood urea level was 21 mg. per 100 ml., and the urine normal.

On April 6 alkaline phosphatase was 32 units per 100 ml., serum calcium 10·5 mg. per 100 ml. and blood cholesterol 187 mg. per 100 ml.

By the end of April the boy's hair was shed in handfuls (Fig. 2). The skin was becoming dry and ichthyotic. The spleen and liver, although reduced in size, were still palpable.

A radiograph of the clavicle on April 25 was normal. The left humerus showed an area of osteoporosis in the upper third of the shaft.

On April 26 the blood carotene level was 20 μg. per 100 ml., and the blood vitamin A 150 i.u. per 100 ml.

On April 27 the blood urea level was 22 mg. per 100 ml., haemoglobin 86%, E.S.R. 12 mm. in one hour. The total and differential white blood counts were normal.

On April 28 the alkaline phosphatase level was 37 units per 100 ml.

On May 23 the blood carotene level was 30 mg. per 100 ml., and the blood vitamin A 90 i.u. per 100 ml.

On May 27 the thymol turbidity was 1 unit per 100 ml. and alkaline phosphatase 26·9 units per 100 ml.

On August 9 the child was well but the liver and spleen were still just palpable. The skin was ichthyotic but the hair was growing well.

Case 2. S.W., a girl aged 4 years, was admitted to the Clayton Hospital, Wakefield, on April 12, 1955. The complaint was of anorexia and malaise, pains in the forehead, wrists, forearms and shins, and facial and temporal swelling for two weeks. There was a loss of weight during the same period. There had been severe epistaxis and also pain and discharge from the ear during the previous two days.

The child had no previous illness apart from ichthyosis for which she had been given 'avoleum', 1 dram t.d.s. (347,280 i.u. per day), from a dermatological department for the past two years.

On admission the child had a temperature of 101° F. She had a scaling, patchy erythematous rash on the upper parts of the arms and trunk. The lips were crusted and bleeding. There was oedema of the eyelids, and the temporal regions were so swollen that the face had a triangular appearance. The shins and forearms were tender to the lightest touch.

The liver was enlarged two fingerbreadths below the costal margin. The spleen was impalpable.

There was a bilateral otitis externa with an underlying otitis media on the right side. The throat was injected.

During the first week in hospital the general condition slowly improved and the temperature was normal in five days. The facial and temporal swelling subsided in three days, but the eruption became more extensive, covering the forearms and abdomen with erythematous patches (Figs. 3 and 4). The skin became dry and scaling and the lips cracked. The tenderness over the long bones became gradually less and at the end of the week there was only slight tenderness over the tibia.

Treatment with penicillin cleared the ear infection. The size of the liver became slightly less.

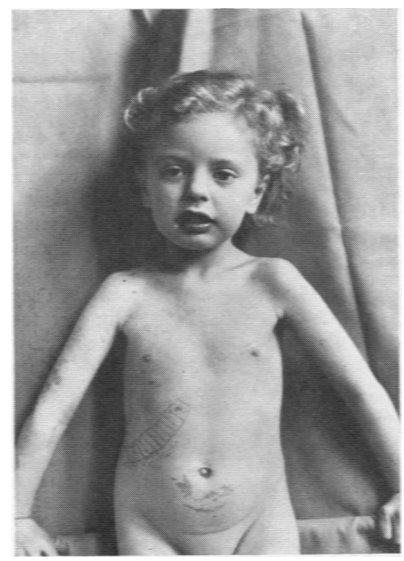

FIG. 3.—Hypervitaminosis A showing macular rash in the acute stage.

On April 13 haemoglobin was 78% (11·6 g.), W.B.C.s 12,800 c.mm. (polymorphs 85%, lymphocytes 13%, monocytes 2%). The B.S.R. was 17 mm. micro in one hour.

The urine showed albumin — and reduced Benedict's

solution. A chromatogram showed glucose. There were a few pus cells and casts.

A swab from the ears on April 14 yielded a heavy growth of penicillin-sensitive *Staphylococcus aureus*.

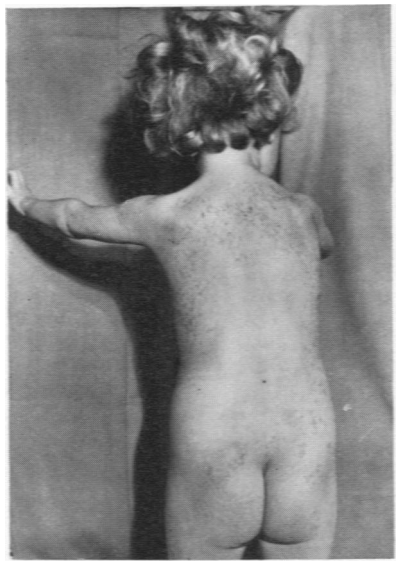

FIG. 4.—Hypervitaminosis A showing macular rash in the acute stage.

Radiographs showed that both mastoid regions appeared normal and a little generalized congestion in the chest.

Radiographs of the wrist and arms on April 15 showed increased density at the growing ends of the shafts of the long bones but no actual irregularity, and no abnormality of the spine and clavicles.

On April 19 the blood carotene level was 20 μg. per 100 ml. and blood vitamin A 700 i.u. per 100 ml.

By the end of two weeks the child was in good general health. The rash and facial swelling had gone but the skin was dry. At the beginning of the third week the hair became dry and lifeless and could easily be pulled out, and soon was shed in handfuls, only a sparse growth remaining. The liver was only just palpable.

On April 26 the blood urea level was 34 mg. per 100 ml. A three-day vitamin C saturation test when 125 mg. ascorbic acid was given each day, gave daily excretions of 2·1, 2·1 and 8·9 mg. (normal for weight 12·5 mg.).

On April 28 the alkaline phosphatase was 41 units per 100 ml., serum phosphorus 3·9 mg. per 100 ml., serum calcium 10·8 mg. per 100 ml. and serum cholesterol 140 mg. per 100 ml.

By July 12, 1955, the hair was growing. The liver and spleen were not palpable. The skin was normal.

On review on November 11 the ichthyosis was returning; the hair was normal and the child well.

Discussion

It has long been known that polar bear's liver produces acute vitamin A poisoning. Rodahl and Moore (1943) found that the vitamin A content of the liver was equivalent to 8,000,000 i.u. in 0·5 kg. The symptoms produced are headache, hyperirritability followed by drowsiness, desquamation of the skin at the mucocutaneous junctions in 24 hours, with peeling of the entire skin in a few days.

Chronic poisoning due to vitamin A has been well described by Caffey (1950 and 1951) following on the earlier descriptions by Toomey and Morissette (1947) and Josephs (1944).

In nearly all the cases described previously the poisoning was due to excessive and prolonged administration of either halibut liver oil or oleum percomorphum. I have not been able to trace any previous record of a case due to a pure vitamin A product such as 'avoleum'.

From the previous accounts a fairly uniform clinical picture can be drawn. The initial symptoms are usually anorexia, fretfulness and itching of the skin. Tender subcutaneous swellings appear over the long bones and skull. Fissures appear on the lips and other mucocutaneous junctions with cracking and bleeding of the mucosa. Cortical thickening of the long bones is usual after the vitamin has been given for six to 15 months. In neither of the above cases was this found, although in Case 2 it was thought that early changes in the long bones could be seen, but the appearances were not very convincing.

The absence of changes in the bones in Case 1 might be due to the fact that a very high dosage was given for only six weeks before symptoms appeared.

Caffey (1950) notes that there is a latent period of several months between the start of the excessive dosage and the appearance of diagnostic clinical signs. The length of this period did not depend on the size of the overdose and the shortest latent period was six months. In his series the earliest radiological observation, showing cortical hyperostosis in the ulnas, was three weeks after the onset of symptoms. It may be that in the two cases described here that as this interval was less than that period the hyperostosis had not time to develop.

Loss of hair and dryness of the skin associated with an erythematous rash also characterize the condition. Both our patients had this typical scaly erythematous rash on the trunk in the early stages of the illness and both lost much of their hair (Fig. 2). After the vitamin A was stopped and the rash had cleared there was a period in which the skin was soft in texture and normal in every way, but this was ultimately followed by a relapse to the ichthyotic

state. This period in which the skin was normal was presumably sustained by the gradual release of vitamin A stored in the liver.

The liver and spleen are often found to be enlarged in hypervitaminosis A and in Case 1 both are still palpable 10 months after admission. This leads one to think that serious and permanent liver damage may be produced by prolonged administration of the vitamin, and makes one wonder whether the possible toxic effects should be lightheartedly dismissed as in some recent statements.

The most characteristic feature of the condition is that once the vitamin A is stopped the signs and symptoms regress and there is rapid recovery. The tenderness, pain, anorexia and irritability usually disappear within one week.

The most valuable investigation is the estimation of the vitamin A blood level showing a rise above the normal level of 50-130 i.u. per 100 ml.

The one condition with which vitamin A poisoning may be confused is infantile cortical hyperostosis. Caffey (1950) pointed out that the latter condition always appears in the first four months of life, whilst hypervitaminosis A is usually not seen before the end of the first year. He states that cortical thickening of the bones is seen in both conditions, the face and jaw are swollen and the mandible thickened in every case of infantile cortical hyperostosis, these structures being unaffected in vitamin A poisoning. The blood levels of vitamin A are normal in cases of infantile cortical hyperostosis.

In conclusion it should be emphasized that the dosage of 'avoleum' recommended by the manufacturers is unlikely to produce symptoms. It would appear that in the treatment of skin conditions by vitamin A care should be taken if it is required to use high dosage for very long periods.

I wish to thank the Editor of the *Proceedings of the Royal Society of Medicine* for permission to publish these cases which were previously reported at the Section of Paediatrics meeting on June 25, 1955 (*Proc. roy. Soc. Med.*, **48**, 1107).

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