Acanthosis nigricans and hypovitaminosis A. Response to topical vitamin A acid

LEOPOLDO F. MONTES¹, BASIL I. HIRSCHOWITZ² AND CARLOS KRUMDIECK³

¹ Departments of Dermatology, ² Internal Medicine, and ³ Pediatrics and Biochemistry, University of Alabama in Birmingham, Medical Center, Birmingham, Alabama, U.S.A.

The pathogenetic mechanisms in acanthosis nigricans are not well known. Hirschowitz et al. (1971) described a new syndrome which included complete nerve deafness, progressive peripheral sensory nerve demyelination, loss of gastric antral motility, multiple diverticula of ileum and lower jejunum, steatorrhea and unusually extensive acanthosis nigricans. Dramatic clinical and histological response of the dermatosis to topical vitamin A acid treatment led to search and demonstration of severe hypovitaminosis A. The trifluoroacetic acid method of Neeld & Pearson (1963), repeatedly used with serum samples, either failed to detect β-carotene and/or vitamin A or showed levels below the normal range. These findings indicate that vitamin A deficiency may be a factor in the pathogenesis of acanthosis nigricans.

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In a recent publication Hirschowitz et al. (1971) described a new syndrome which affected three teenage sisters and included: complete deafness, peripheral sensory nerve demyelination, loss of gastric antral motility, multiple diverticula of ileum and lower jejunum and steatorrhea. In addition, two of these sisters developed an unusually extensive acanthosis nigricans. This report describes this dermatosis, the recent demonstration in one of these patients of severe hypovitaminosis A, and the response of the acanthosis nigricans to topical vitamin A acid treatment.

Case Report

Born in 1949, after a normal pregnancy, this patient began to have hearing loss at age 3, and was completely deaf at age 5. At age 15 she began to have abdominal cramps with diarrhea and vomiting of food retained 24 hours, and over the next year gradually lost weight from 37.6 kg to 26 kg. The description of 3–5 bowel movements per day suggested steatorrhea. She had intermittent pedal edema, anorexia and her periods had stopped 6 months before, previously having being regular since age 13.

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On our initial examination she was very thin, but had no skin lesions (these were to develop later). Abdomen showed hyperactive small bowel and a distended stomach with a succussion splash. Apart from gross muscle wasting the extremities were normal and she did not have pes cavus. Her growth had been normal, with secondary sex characteristics normal for her age. Neurological examination confirmed bilateral nerve deafness, and showed absent knee and ankle jerks. Sensation was intact; her speech was rudimentary but she could read and write very well (I. Q. 88). Audiometry showed 70 decibel loss at 125–250 Hertz and 110 decibel loss at 500–2000 Hertz.

Laboratory studies. PCV 40 %, WBC 19,000. A 4-day fat balance showed stool excretion of 9 g fat and 2.1 g N₂ per day from an average daily intake of 25 g protein and 46 g fat. Duodenal biopsy was normal both by dissecting and light microscopy. Absorption studies included normal xylose (16% excretion in 5 hours, 10 g oral dose); a low normal but delayed rise glucose tolerance, normal lactose tolerance, prothrombin time 91%, serum Fe++ (32 mcg %), whole blood vitamin B₁₂ (220 pg/ml), whole blood folate 37 ng/ml and Schilling test (3.6 %). Exocrine secretion tests were normal. Gastric secretion: basal H⁺ output 1.1 mEq/h, after histamine 12.5 mEq/h. pancreatic test with secretion and pancreozymin (14 mEq HCO₃⁻/h), sweat Cl⁻ (33 mEq/l). Normal esophageal motility by manometric testing was observed. Gastric motility by x-ray was grossly diminished. X-rays also revealed marked gastric distension and retention, and grossly abnormal small bowel including a suggestion of linear ulceration.

Special fat absorption studies. A long chain (C-18) (oleic acid) and a short-chain (C-8) (octenoic acid)* both labelled with ¹³¹I were utilized. Her younger sister, then apparently normal, was used as control.

Of the ¹³¹I oleic acid, 41% was lost into the stool in 24 h and 44% at 72 h; by contrast only 2% of the ¹³¹I octenoic acid was recovered from the stool in 72 h, indicating normal absorption of short-chain fatty acid via blood, but malabsorption of long-chain fatty acids via the lymphatics. In the control subject 2% of either fat appeared in the stool in 72 h.

Laparotomy. After the diagnosis of multiple diverticula was made in the elder sibling at autopsy, and because of the virtual identity of their clinical picture, diagnostic laparotomy was performed on 1/15/66. Though the stomach and first part of the duodenum were markedly dilated, no obstruction was found. The small bowel was almost exactly as in the elder sibling (Hirschowitz et al. 1971). The mesentery was thickened with very large lymph nodes, and was especially hyperplastic at the attachment to the ileum and lower jejunum. The ileal mucosa contained linear ulcerations along the mesenteric attachment. In a 5 cm resected specimen a diverticulum and two discrete ulcers were seen. Culture of the ileal ulcers grew a heavy growth of *Clostridium perfringens*, sensitive to ampicillin but not tetracycline.

Continuing gastro-intestinal disease. In the succeeding year she maintained her weight at about 33 kg but had persistent gastric retention, intermittent vomiting and abdominal cramps with infrequent bouts of diarrhea. In July 1967, a "Jaboulay pyloroplasty" was performed but the gastric retention was unrelieved by this procedure and again little or no motility was evident on x-ray. Four months later, progressive intestinal obstruction developed and a 70 cm section of mid-ileum had to be resected.

However, she failed to improve and her

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* Octenoic acid was kindly supplied by Dr. Fred Snyder, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.
weight, which had been 30 kg before surgery, again dropped to 25 kg mainly due to extreme anorexia. She failed to respond to antibiotics combined with a rigorous medium-chain triglyceride diet. Prednisone in initial doses of 20 mg/day resulted in gradual improvement and by November 1967 she again weighed 33 kg and in December menstruation returned. In February 1968 she weighed 40 kg and developed a perforated nasal septum. She remained well with progressive weight gain despite persistence of the gastric retention. She returned to school and completed the 10th grade. By November, 1968 she weighed 43 kg, was taking only 7.5 mg prednisone per day, had reduced MCT to less than 25% of fat intake and was having no diarrhea. At this time rapidly progressing acanthosis nigricans had developed and involved, in unusually extensive fashion, many areas of the skin.

Neurological disease. Apart from the deafness, initially the only obvious neurological deficit was general hyporeflexia with absent ankle and knee jerks. In 1965 at age 16, sensation — pinprick, touch, vibration, position — was normal.

In November 1967 she was noted to have early loss of sensation in the Achilles tendons, fingers and toes. Decreased corneal reflexes and more sluggish reflexes with loss of the abdominal reflexes became apparent but she retained flexor plantar responses.

By May 1970 she began to notice damage to the finger tips from trauma sustained but not felt in making artificial flowers. At this time, in May 1971, the abdominal reflexes and the tendon jerks in the legs could not be elicited, and the arm jerks were very weak. Pin prick, but not touch, could be perceived in the fingers and trunk but not below the knees. Vibration and position sense were preserved. In April 1972 she had lost all sensation up to one thigh and was developing Charcot's joint in one knee.

Biopsies of the sural vein and nerve were performed in 1970. The fragment of sural vein showed extremely thickened walls and narrow lumen. The most important component was sclerosis of all three layers, and prominent hyperplasia of smooth muscle cells in the subintima. There was no inflammation or scarring.

The fragment of sural nerve showed marked atrophy of the nerve bundles, separated by, and encased in, a thick layer of fibrous tissue. Demyelinization of the nerve fibers was almost universal with only very occasional myelin coats preserved and even these showed vacuolization and fragmentation. The axons were much better preserved, but they varied greatly in thickness, showed variations at the level of individual elements, and were generally without myelin coats. Macrophages, loaded with fatty debris, were prominent in between fibers and around vessels. The changes were very similar to those reported in peripheral sensory neuro-

Fig. 1A. Right axilla showing acanthosis nigricans prior to treatment. Notice the site of a punch biopsy (depigmented area).

Fig. 1B. Microscopic view of skin shown in Fig. 1A. The epidermis is characterized by irregular folds filled with keratin. The papillae are arranged as finger-like projections. Hematoxilin and eosin, × 250.

Fig. 1C. Right axilla as seen 4 weeks later, following daily topical treatment with 0.1% retinoic acid ointment b.i.d.

Fig. 1D. Microscopic view of skin shown in Fig. 1C. The features of acanthosis nigricans have been replaced by marked hyperplastic stratum spinosum and disappearance of the superficial folds. The stratum corneum is thinner. Hematoxilin and eosin, × 250.
pathy. If the tachycardia and loss of gastric motility could be interpreted as evidence for vagal nerve involvement, this preceded peripheral sensory loss by 3 years.

Acanthosis nigricans. When first seen in consultation by one of us (LFM) on November 27, 1968, the patient displayed marked and extensive acanthosis nigricans involving axillae (Fig. 1A), groins, popliteal fossae, antecubital areas, neck, lower chest and practically the entire abdominal region. Interestingly, the laparotomy incision sites remained unaffected (Hirschowitz et al. 1971). Several punch biopsies revealed the typical histologic picture of acanthosis nigricans (Fig. 1B). In some areas of the skin which were not affected by the acanthosis nigricans, such as the face and extremities, hirsutism was present. Because of 1) the hyperkeratotic nature of acanthosis nigricans, 2) the favorable response of other hyperkeratotic dermatoses to topical retinoic acid (vitamin A acid), and 3) the extremely low β-carotene levels found in this patient, a therapeutic trial with topical retinoic acid seemed justified. The preparation employed was an ointment containing 0.1% retinoic acid.*

The patient was instructed to apply the ointment twice daily on the entire right axilla. The left axilla as well as other involved areas were initially left untreated in order to serve as controls. An immediate response to treatment occurred. On the first follow-up visit 2 weeks later, marked improvement of the acanthosis nigricans had occurred. The patient was instructed to continue treatment, and 4 weeks later there was marked improvement with almost complete resolution of the hyperkeratotic verrucous lesions. The previously affected right axilla showed only discrete erythema (Fig. 1C). The left axilla and other initially untreated areas remained unchanged. A punch biopsy taken from the treated area showed a completely different histologic picture than before the treatment. The hyperkeratosis was markedly reduced: the characteristic, finger-like projections of the papillae had disappeared due to a general hyperplasia of the stratum spinosum (Fig. 1D).

Treatment was later extended to all the previously untreated areas and similar response occurred. In view of this striking clinical and histologic response, the question arose as to whether or not a deficiency in vitamin A could be a factor in the pathogenesis of the acanthosis nigricans. At this time determinations of serum levels of both vitamin A and β-carotene had been started in our Medical Center by one of us (CMK), thus a study was undertaken to determine the serum levels of these two substances as well as the effects of parenteral administration of vitamin A on this patient.

Vitamin A studies. Vitamin A and β-carotene serum levels were determined employing the trifluoroacetic acid method of Neeld & Pearson (1963). Repeated determinations failed to demonstrate detectable amounts of vitamin A in the serum or revealed levels below the normal range. Likewise, β-carotene was either undetectable or below the normal range. A short therapeutic trial of vitamin A given intramuscularly was carried out in an attempt to establish whether a correction of the hypovitaminosis A could produce improvement of the acanthosis nigricans, hypovitaminosis A and other abnormalities. This trial is summarized in Fig. 2. An increase in vitamin A serum levels was gradually achieved. Interestingly, β-carotene levels which prior to treatment had often been reported as zero also began to rise. This trial had to be discontinued after 2 months because the patient required further surgery (gastroenterostomy) due to increasing gastric retention. However, the patient continued to apply vitamin A acid on

* Retinoic acid ointment was supplied by Dr. F. Wortham, McNeil Laboratories.
ACANTHOSIS NIGRICANS AND HYPOVITAMINOSIS

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<th>Vitamin A * (μg/100 ml)</th>
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Fig. 2. Dose schedule of intramuscular vitamin A and resulting serum levels of vitamin A and β-carotene.

the previously affected areas and the acanthosis nigricans did not recur.

**Discussion**

Acanthosis nigricans may present itself as a genetic defect, may develop in association with malignant disease (Curth 1971), may be related to endocrine and metabolic disorders (Brown & Winkelmann 1968, Reed et al. 1968) or may be iatrogenic in nature (Shelley 1972). Our patient should be included in the first group but was unusual because of the extensive fashion in which the dermatosis involved the skin.

Histologically, acanthosis nigricans shows striking evidence for an abnormal process of keratinization. In turn, defective keratinization is one of the salient features of vitamin A deficiency in man and in animal. Thus, it seems logical to propose that the vitamin A deficiency may be a factor in the pathogenesis of acanthosis nigricans.

Interestingly, vitamin A deficiency in animals (Moore 1967) was found to cause degeneration of myelin and complete deafness, a salient feature in this patient. The increase in β-carotene serum levels, often reported as zero, in response to parenteral or oral vitamin A administration, suggests that a very active conversion of carotenes to vitamin A must be taking place continuously in this patient. It seems possible that when the levels of vitamin A are increased by outside supplementation, it results in a sparing effect of the carotene.

The striking epidermal changes induced by topical retinoic acid, reduction of hyperkeratosis and increase in thickness of stratum spinosum, confirm the findings of Kligman et al. (1969). These investigators demonstrated that topical retinoic acid does not have the antikeratinizing effect earlier hypothesized. On the contrary, it induces an increase in epidermal mitotic activity which in turnresults in the production of less cohesiveness of horny cells, enabling them to dehisce.

It should be remembered, however, that retinoic acid has also other known effects which suggest a more complex mechanism of action. Although it has no role in reproduction, it is fully effective in other systemic roles of vitamin A. A normal metabolite of retinol (Fig. 3), it can replace vitamin A in many biological processes such as growth, sulfurylation of phenols and mucopolysaccharides, and metabolism of adrenocorticosteroids. Furthermore, it promotes the growth of vitamin A depleted animals and this is a prolonged effect (Moore 1967, De Luca & Suttie 1969).
Fig. 3. Summary of the metabolism of vitamin A in humans.

References


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