

Leg Cramps (Systremma) and "Restless Legs" Syndrome

Response to Vitamin E (Tocopherol)

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■ *A clinical investigation into the therapeutic value of vitamin E (tocopherol) in certain dermatological conditions of obscure etiology led to the incidental observation that this compound produced beneficial effects in some of the patients who were suffering from frequent and severe nocturnal leg cramps. Nearly all of the patients with leg cramps received prompt and gratifying relief from their symptoms while taking vitamin E in the form of d, alpha-tocopheryl acetate, 100 I.U. three times a day before meals. The group included 24 private patients with leg cramps and two with the "restless legs" syndrome, probably a related condition. One of the patients with leg and foot cramps also had severe nocturnal rectal cramps which were also relieved.*

Nocturnal leg cramps constitute a relatively common complaint in the general practice of medicine and may be very distressing to the patient. Not only is the cause obscure and the treatment relatively unsatisfactory, but even its proper medical name, systremma (anything twisted up together), is unknown to most physicians.

THE PRESENT STUDY originated as a by-product of an investigation into the usefulness of vitamin E in the management of several obstinate dermatological conditions, especially pseudoxanthoma elasticum and epidermolysis bullosa.¹

Since the discovery of vitamin E nearly 46 years ago, a large volume of literature on it has accumulated, including hundreds of reports of animal and

laboratory experiments, clinical investigations and at least five international conferences, two of which were sponsored by the New York Academy of Sciences.

Inasmuch as this vitamin plays an essential role in practically all body tissues in protecting vital cell membranes and intracellular structures from damage by lipid peroxidation (antioxidant effect) and possibly also in facilitating activation of certain enzyme systems, a breakdown either in supply, absorption or utilization of vitamin E might be expected to produce a wide spectrum of symptoms and disease processes.^{2,3,4,5,6}

One of the most commonly observed manifestations of a vitamin E-deficient diet in many experi-

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TABLE 1.—*Systemema (Leg Cramps) Treated with Vitamin E (Tocopherol)*

| Case | Sex and Age | Duration | Frequency | Severity | Treatment Daily Dose | Results | Comments |
|------|-------------|----------|---------------------------|---------------------|------------------------------|-----------|--|
| 1 | M 70 | 1 yr. + | Nightly or oftener | Severe arms & legs | 300 IU 2 mo. | Excellent | Only 1 cramp in 2 mo. |
| 2 | M 84 | 10 yr. | Nearly every night | Severe 5-10 min. | 300 IU 3 mo. | Moderate | Letter from patient: "Cramps have diminished" |
| 3 | F 78 | 20 yr. | Nightly or sev. × a night | "Jumpy legs" severe | 300 IU 2 mo. | Excellent | "Restless legs" syndrome complete cure; unresponsive to Dilantin® and Benadryl® |
| 4 | M 61 | 1 yr. | Every other night | Severe | 300 IU 3½ mo. | Excellent | Complete control. Only partially controlled with quinine. |
| 5 | M 77 | 5 yr. | 2 × a week | Severe 15 min. | 300 IU 3½ wk. | Excellent | Complete control |
| 6 | F 28 | 1½ yr. | Every night | Severe at times | 300 IU 2 mo. | Excellent | Marked improvement. Quinine, Librium® and muscle relaxant previously ineffective |
| 7 | F 60 | 3 wk. | Every night | Severe | 300 IU 2 mo. | Excellent | Complete control |
| 8 | M 57 | 5 yr. | 1 or 2 × a month | Moderate 5 min. | 300 IU 2 mo. | Excellent | Complete control |
| 9 | M 76 | 6 yr. | 2 or 3 × a week | Moderate | 300 IU 2 mo. | Moderate | Cramps reduced about ¾ |
| 10 | M 88 | 2 yr. | Every other night | Severe 10 min. | 300 IU 2 mo. | Excellent | Cramps at night and also after walking. Reduced to 2 or 3 times a month. |
| 11 | F 32 | Sev. yr. | 2 × mo. | Severe 15 min. | 300 IU 4½ mo. | Excellent | Complete control |
| 12 | F 49 | 5 yr. | 3 × wk. | Severe | 300 IU/1 mo. 100 IU/1 mo. | Excellent | Only 1 cramp in 2 mo. |
| 13 | M 75 | 3 yr. | Every other mo. | Severe 15-20 min. | 200 IU 1½ yr. | Excellent | Complete control |
| 14 | F 74 | 3 yr. | 3-4 × wk., sev. × a night | Severe 15 min. | 200 IU 1½ yr. | Excellent | 99% control |
| 15 | M 60 | 15 yr. | 2 × mo. | Severe 10-15 min. | 300 IU 3 mo. | Excellent | Complete control |
| 16 | F 70 | 5 yr. | 1 or 2 × mo. | Moderate | 300 IU 5 mo. | Excellent | Cramps in feet. Complete control. |
| 17 | F 80 | Sev. yr. | Nightly | Severe | 300 IU 3 mo. | Excellent | Only 3 minor cramps in 3 mo. Quinine ineffective. |
| 18 | F 25 | Sev. yr. | 1 × wk. | Mild | 300 IU 2 mo. | Excellent | Complete control |
| 19 | F 68 | 3 yr. | 2 or 3 × a wk. | Severe | 300 IU 6 wk. | Excellent | Had severe nocturnal rectal cramps, as well as foot cramps. Both controlled. |
| 20 | F 58 | Many yr. | 2 × mo. | Mild | 300 IU 7 mo. | Moderate | Only 2 mild cramps in 3 mo. |
| 21 | F 60 | 3 yr. | 3 × mo. | Moderate | 300 IU 9 mo. | Excellent | Only 2 or 3 minor cramps in 9 mo. |
| 22 | F 68 | 3 yr. | 2 × wk. | Moderate | 300 IU 2 mo. | Moderate | Only occasional cramp after unusual exercise. |

(Table 1 is continued on next page)

Continuation of Table 1.—*Systemma (Leg Cramps) Treated with Vitamin E (Tocopherol)*

| Case | Sex and Age | Duration | Frequency | Severity | Treatment Daily Dose | Results | Comments |
|------|-------------|----------|---------------------|---------------------------|------------------------------|-----------|--|
| 23 | F 61 | 10 yr. | Nightly | Severe 5 min. + | 300 IU 5 wk. | Excellent | After 5 wk. only 1 or 2 × a wk. Very mild. |
| 24 | F 26 | 2 yr. | 2 or 3 × nightly | Severe | 300 IU 4 wk. | Excellent | No cramps after 2 wk. |
| 25 | F 37 | 10 yr. | Nightly | "Restless legs" severe | 300 IU/6 wk. 200 IU/4 wk. | Excellent | Complete relief |
| 26 | F 78 | Sev. yr. | Nightly | Severe ½ hr. | 300 IU/3 da. 100 IU/6 wk. | Excellent | Almost complete relief |

mental animals, including the rhesus monkey, is an acute and extensive degenerative change in skeletal muscles and, in some instances, in cardiac muscle.⁷

Early in our dermatological study several patients mentioned that they had suffered from severe nocturnal leg cramps but that after they began taking vitamin E their leg cramps had ceased. The experimentally induced muscle damage resulting from a vitamin E-deficient diet suggested the possibility that nocturnal leg cramps might be caused by either a mild deficiency or faulty utilization of this vitamin in the leg muscles.

Encouraged by these results, we began to question all the patients in our study, as well as all new patients, regardless of their skin problems, concerning a history of leg cramps. As a result, a total of 24 patients with leg cramps and two with "restless legs" syndrome were given d, alpha-tocopheryl acetate, 100 I.U. three times a day before meals.* Nineteen of these 26 patients had symptoms classified as severe, five as moderate and two as mild. Excellent results (90 to 100 percent relief) were obtained in 22 patients and moderate improvement in four. Relief was prompt, usually occurring within the first week or two, suggesting therapeutic specificity. No other drugs were given. Two patients who had obtained almost complete relief discontinued the vitamin after about two months. There was a gradual return of symptoms within four or five weeks in both patients, but the cramps disappeared again on resumption of medication. It probably would be possible to reduce the dose to 200 or 100 I.U. per day after the condition has been brought under control.

*It is important in prescribing the vitamin that it be taken at least 10 or 15 minutes before mealtime and that it not be administered simultaneously with medication containing iron, and mineral oil should also be avoided, since iron and mineral oil tend to lessen the absorption of vitamin E.

The brand which the authors have used most often is manufactured by Professional Drug Products, Los Angeles, California, and is distributed by Horton & Converse, 2005 Wilshire Blvd., Los Angeles, Ca. 90057. U.S.V. Pharmaceutical Corporation (formerly U.S. Vitamin Corp.) also produces a brand called Aquasol® E, which is a water-solubilized form useful for persons who are unable to tolerate or absorb fats, since vitamin E is normally a fat-soluble vitamin.

One of these patients, a 78-year-old woman, instead of having actual cramps complained of "restless legs," or as she expressed it, "jumpy legs," which had bothered her severely for 20 years, interfering with sleep nightly and only partially relieved by Dilantin® and Benadryl®. She received complete relief with the vitamin E. Another patient, a 37-year-old woman who nightly for ten years had been troubled with "restless legs" to the point of interference with sleep, obtained complete relief after two weeks of vitamin E therapy, and the improvement has been maintained on 200 I.U. daily. One patient in this series, a 68-year-old woman, in addition to having frequent leg and foot cramps also had severe nocturnal rectal cramps, necessitating the application of heat. Both manifestations responded to vitamin E (See Table 1).

Discussion

A review of the literature on leg cramps failed to disclose any scientific name for this entity. Mrs. Helen Tibbs, of the Los Angeles County Medical Library staff, after consulting various cross-references, came to our rescue with a copy of Dorland's Medical Dictionary, 20th Edition, where "systemma" was defined as "cramps in the calf of the legs," from the Greek, meaning "anything twisted up together." We herewith submit "systemma" as a proper term not only for leg cramps but for cramps involving other muscle groups as well.

Most current texts on internal medicine and orthopedic surgery give scant attention to nocturnal leg cramps, despite the fact that it is recognized as a fairly common complaint. According to Perchuk,⁸ "Nocturnal leg cramps are symptomatic of an abnormal muscle metabolism and are present in a variety of conditions. Although the calf is generally involved, other muscle groups may be affected, and as illustrated in one case history, even the upper extremity may be the site of nocturnal cramps." Perchuk and coworkers⁹ obtained grati-

fyng relief by oral administration of a muscle relaxant, methocarbamol (Robaxin®) in which "therapy was based on the drug's ability to suppress reflex skeletal muscle spasm at the level of the spinal cord. Thus, proprioceptive stimuli arising out of ischemic conditions, imbalances in metabolism or calcium-phosphorus imbalance are blocked before they are able to trigger clonic or tonic contractions."

Perhaps vitamin E may correct the metabolic defect at its source without the necessity of any blocking action. Any medication which is able to restore normal function with no risk of serious side-effects would appear to be suitable.

Leg cramp is a frequent complication of pregnancy, according to Salvatore,¹⁰ who reported an incidence of 33 percent in a series of 980 pregnant women. In 6.1 percent the cramps were severe enough to require treatment.

There have been a number of papers on "restless legs," beginning with Allison's¹¹ and including papers by Tatlow,¹² Masland,¹³ Ekbohm,¹⁴ De Jong,¹⁵ Gorman, et al,¹⁶ and Roberts.¹⁷ While leg cramps and "restless legs" are usually dealt with as separate entities, certain features, especially the site, the muscles involved and response to treatment, suggest a close relationship. Etiologic explanations and therapeutic achievements in both conditions have left much to be desired.

Roberts,¹⁷ in a comprehensive paper based upon clinical and laboratory investigations of 131 patients affected with spontaneous leg cramps (SLC) and restless legs (RL), offers convincing evidence that these manifestations, frequently occurring in the same patient, are part of the same process and are caused by extremely low blood sugar levels due to diabetogenic hyperinsulinism (DH), which he considers to be a precursor to true diabetes.

Returning to our own modest series of 26 cases of leg cramps (systemma) and "restless legs," no laboratory studies of any kind were carried out, and the cases are presented merely as an interesting clinical observation. In view of the brilliant results obtained with a simple therapeutic agent without any drugs to block nerve impulses or dietary management, one cannot but speculate on exactly what the mode of action of vitamin E may be in relieving leg cramps. At least two contributions^{18,19} indicate that tocopherol improves glycogen storage in the muscles.

Tocopherol is a fat-soluble vitamin composed of a number of fractions. Many investigators have

shown that for all practical purposes the alpha fraction is so much more physiologically active than all the other fractions, the latter can be ignored and deficiency states produced by vitamin E-deficient diets can be corrected by giving alpha-tocopherol alone. The use of mixed tocopherols merely dilutes the effectiveness of the preparation.

Again, the acetylated form protects the vitamin from premature oxidation before being absorbed through the intestinal wall. Vitamin E is absorbed much more effectively if it is taken on an empty stomach, at least 10 or 15 minutes before meals. The natural vitamin is more potent than the synthetic. The designation d, alpha-tocopheryl acetate specifies the acetylated form of the natural alpha fraction of tocopherol. An average adult dose is 100 I.U. (not mg) three times a day before meals. For persons unable to absorb fats, a water-solubilized form, Aquasol E, is available. Diets high in polyunsaturated fats increase the requirements for vitamin E, as does the simultaneous administration of iron. The frequent use of laxatives, especially mineral oil, interferes with the absorption of vitamin E.

Serious side-effects are virtually nil. Because of the observed tendency of vitamin E to improve glycogen storage in the muscles, diabetic persons who are taking insulin should probably be started on smaller doses, which can be gradually increased as the insulin dosage is adjusted. Patients with severe hypertensive heart disease should also be started on smaller doses, although the hypertension may later be benefited.

Quinine, which is usually prescribed for this condition, is only partially effective and always carries the possibility of unpleasant side-effects. Tocopherol plays an important role in intracellular enzyme and antioxidant processes of various tissues, and an adequate supply appears to be essential for the physiological functioning of muscle tissues. The fact that the leg muscles are undergoing cramps or spasms even while at rest suggests a lack of some essential factor, and the prompt relief afforded by tocopherol may indicate an inadequate supply, inadequate absorption or defective utilization of this vitamin.

Although placebo studies would have made the results here reported more impressive, they were not carried out because none of the patients consulted us for the leg cramps, and the observations reported in this study were coincidental to an investigation into the value of tocopherol in certain

dermatological conditions. For these reasons no detailed medical studies pertaining to the circulatory system or blood chemistry were done. Even so, it was felt that a brief clinical report might be of assistance to others wishing to carry out more detailed investigations into this common and painful disorder for which no really effective treatment is at present available.

TRADE AND GENERIC NAMES OF DRUGS

- Aquasol*® E d, alpha-tocopheryl acetate (aqueous vitamin E)
- Benadryl*® diphenhydramine hydrochloride
- Dilantin*® diphenylhyantoin
- Librium*® chlordiazepoxide hydrochloride

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TRICKS IN TUBAL INSUFFLATION

"One of the little tricks in tubal insufflation is to insert the uterine cannula, holding it with the left hand, and press the uterus down against the cannula—thus occluding the cervix without the use of a tenaculum. The interesting thing that happens is that as the gas passes through the tubes and bubbles up against the peritoneal surface on the top, one can feel a little sense of crepitation. This is very comforting because sometimes you hear gas and sometimes you don't; sometimes it's on one side, sometimes on the other. But this crepitation almost assures you that gas has passed through.

"Incidentally, in doing tubal insufflations, one is wise to flush out the long tube from the instrument to the cannula with carbon dioxide before starting the test. If you don't, then what you are really insufflating with is common air because that's what goes in and probably goes through the tubes long before the carbon dioxide from the machine even reaches the cannula. If you use air, then the patient has much more prolonged shoulder pain than if you use gas."

—PENDLETON TOMPKINS, M.D., San Francisco
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