Topical Treatment of Sjögren-Larsson Syndrome with Calcipotriol

Abstract

Two patients with Sjögren-Larsson syndrome were treated with calcipotriol in ointment and the ointment base only for 12 weeks, using a double-blind bilaterally paired comparative study. Unilateral improvement was observed in both patients in favour of the calcipotriol-treated side. The present case is the first demonstration of a substantial clinical effect of calcipotriol in the Sjögren-Larsson syndrome.

Introduction

The Sjögren-Larsson syndrome (SLS) is a rare, autosomal recessively inherited disorder with an estimated incidence of 1:200,000. Characterizing features of this neuro-ectodermal genodermatosis are ichthyosis and neurologic manifestations, while a number of associated symptoms may be present. The outstanding clinical feature of ichthyosis in SLS is the congenital, yellowish to dark brown, keratotic lichenification of the skin. Signs of the neurologic manifestations, i.e. pathologic reflexes, muscular hypertonia, spastic di- or tetraplegia and mental retardation, usually emerge between 4 and 30 months of age and are stationary after puberty [1]. High-field magnetic resonance imaging may reveal atrophic changes of the cerebral motor area, extrapyramidal system, corpus callosum and spinal cord [2]. SLS may be associated with a variety of other anomalies. The presence of glistening dots on the macular region of the retina is regarded as pathognomonic, although not present in all patients. These dots are due to focal microglial degeneration and lead to impaired central vision [3, 4]. Amblyopia may further reduce visual acuity [5]. Hyperkeratosis of palms and soles as well as joint hyperextensibility have been reported in association with the SLS [6].

Biochemically, a deficiency of the fatty aldehyde dehydrogenase component [7] of the fatty alcohol:NAD+ oxidoreductase complex has been established in cultured fibroblasts and leucocytes [8, 9], while a partial reduction has been reported in obligate carriers [10]. Using a histochemical technique, a deficiency of fatty alcohol:NAD+ oxidoreductase activity in the epidermis and jejunal mucosa has been demonstrated [11].

This enzyme deficiency may constitute the biochemical link between the skin and neurologic symptoms, for fatty alcohol:NAD+ oxidoreductase deficiency causes accumulation of fatty alcohols in keratinocytes and neurons. The fatty alcohols are subsequently incorporated into lipids essential for normal cell membrane functions. Recently, however, 2 patients with the typical clinical features of SLS have been reported with normal fatty alcohol:NAD+ oxidoreductase activity, possibly suggesting that SLS is a heterogeneous disease [12, 13].

Vitamin D₃ (dihydroxycholecalciferol) causes a dose-dependent decrease in proliferation and an increase in differentiation of human cultured keratinocytes [14]. Clinical data indicate that externally applied vitamin D₃ is effective in alleviating psoriasis, where proliferative activity of the epidermis is greatly increased [15]. This study was part of a
large multicentre study [16] and was intended to be an illustration of the effect of calcipotriol in SLS.

Patients and Methods

Since the age of 10 months, a 35-year-old man had shown an ichthyosis with a yellow to brownish lichenified appearance, particularly pronounced on the flexural surfaces and on the lower abdomen. In childhood a spastic diplegia, impaired vision and photophobia became manifest. His 38-year-old sister had a similar skin condition, though less extensive, without neurologic or ophthalmologic complaints. Funduscopic examination revealed a brightened macular region of the retina in both patients. Pathognomonic small glistening dots were observed only in patient I (fig. 1). Histologic findings consisted of orthokeratosis, focal parakeratosis, acanthosis and focal papillomatosis of the epidermis. To confirm the clinical diagnosis, a biochemical assay was carried out, measuring the fatty aldehyde dehydrogenase component of fatty alcohol:NAD+-oxidoreductase in cultured fibroblasts. The assay was carried out as described by Rizzo and Craft [7] using hexadecanal as substrate. Fatty aldehyde dehydrogenase values were 496 and 1,486 pmol/min/mg protein (normal range 3,320–4,850) in patients I and II, respectively, and confirmed the clinical diagnosis.

The 2 patients were treated with topical calcipotriol after informed consent had been obtained. Topical (aqueous 10%) as well as systemic treatment (acitretin 10 mg daily) was stopped 2 and 10 weeks, respectively, before the treatment was started. To make sure that any effect of previous topical therapy disappeared, the patients only used an emollient (Locobase) as required, in the pretreatment wash-out period of 2 weeks. Using a double-blind, bilaterally paired comparative approach, the patients received calcipotriol ointment (50 μg/g) on one side of the body and the vehicle only on the opposite side. The ointments were applied thinly and evenly, twice daily, for a period of 12 weeks. A maximum amount of 120 g ointment per week was dispensed for each side of the body. The patients were instructed to wash their hands after application, to avoid inadvertent spread to other body areas. Blood samples for haematological and biochemical analysis were taken 2 weeks before the start of the study and at weeks 2 and 12 of the treatment phase. Clinical efficacy was established by measuring the extent of roughness, using a 4-point scale.

Results

At the end of the study, a half-side reduction, in favour of the calcipotriol-treated side, was observed in both patients (fig. 2, 3). No improvement was observed at the ointment-base-treated side. Apart from some discomfort at both sides due to the fatty base, no unilateral side-effects were reported. Blood parameters remained in the normal range during the study. In particular, there was no rise in serum calcium. Roughness appeared to be the best parameter to establish clinical improvement of the ichthyosis, characterized by keratotic lichenification, in SLS. Erythema and scaling, however, were absent in both patients at the start of the study and remained so till the study was completed.
Discussion

This is the first demonstration of a therapeutic effect of topical calcipotriol in the SLS. In the present study, no clinical side-effects or laboratory abnormalities were found. Previous reports on topical treatment with 1α,25-dihydroxyvitamin D₃ as well as systemic treatment with 1α-hydroxyvitamin D₃ of autosomal dominant ichthyosis vulgaris (ADIV) and X-linked recessive ichthyosis (XRI) showed an ineffectiveness of vitamin D₃, [17, 18]. Frost [19] established hyperproliferation to be a contributing factor in the pathogenesis of lamellar ichthyosis and epidermolytic hyperkeratosis, but not in ADIV and XRI, using autoradiographic techniques with tritiated thymidine which is incorporated into cells in the period of DNA synthesis. Jagell and Liden [20] demonstrated the DNA synthesis of epidermal cells in SLS to be 2.7 times greater than normal, using the same technique. Therefore, the ichthyosis in SLS is characterized by hyperproliferation, whereas ADIV and XRI represent normoproliferative ichthyoses, possibly explaining the differences in clinical efficacy of the treatment with vitamin D₃ analogues.

Apart from symptomatic therapies improving skin manifestations, a substitutional treatment has been proposed, in order to correct the basic lipid disorder underlying both dermatologic and neurologic symptoms [21, 22].

An interesting speculation is the possible amelioration of the neurologic symptoms by supplementation of dopamine agonists, since severely reduced dopamine concentrations have been found in the putamen and, to a lesser extent, in the substantia nigra and other striatal regions suggesting a specific monoaminergic dysfunction in patients with SLS [23].

Further research remains to be done, in order to offer the patient with SLS a substitutional treatment, ameliorating both skin and neurologic symptoms. At the moment though symptomatic treatment of the skin manifestations remains important. Topical calcipotriol constitutes a new and promising approach in alleviating the ichthyosis in SLS.

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References


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