Cold-sensing ameliorated ichthyosis in a patient with Dorfman-Chanarin syndrome likely through reversed lypolysis under thermo-regulation in keratinocytes

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Introduction

Dorman-Chanarin syndrome (DCS) is an autosomal recessive, neutral lipid storage disorder with ichthyosis to loss-of-function mutation in *CGI-58*, characterized by the presence of intracellular lipid droplets in cells of multiple organs. CGI-58 is an activator of adipose triglyceride lipase (ATGL) contributing to triglyceride (TG) lipolysis. Here, we report a case of 71-year-old man with DCS, presented ichthyosiform erythroderma with a distinct seasonal variation. His skin lesions were aggravated in summer but resolved spontaneously during winter. Biochemical analysis of scales from his lesions revealed increased levels of TG and decreased levels of fatty acids (FA), indicating dysfunction of ATGL. Notably, the patient showed higher levels of TG but lower FA in the scales taken in summer than those in winter, suggesting that ‘seasonal’ fluctuated activity of ATGL might be associated with the clinical severity (J Dermatol Sci 2010; 57: 102). We also demonstrated that diseased scales showed acylceramide deficiency and this might contribute to ichthyosis phenotype (J Invest Dermatol 2010; 130: 2497). Strikingly, topical application of menthol containing pasting resulted in local resolution of his ichthyosiform lesions. Since menthol is an agonist of transient receptor potential M8 (TRPM8), which is activated by low temperature below 25°C. We now speculate that temperature-dependent mechanism may be involved in the etiology of DCS in this specific patient.

Case presentation

1) (a) Scaly ichthyosiform erythroderma. (b) Sharply demarcated site of uninvolved Skin on the lateral aspect of the upper arm. (c) Large, membranous scales on the leg.

2) Histological appearance and lipid deposition in epidermis and blood cells. (a) Hyperkeratosis, mild acanthosis and the normal granular layer. (b) Staining with oil red O demonstrated lipid droplets within keratinocytes in stratum granulosum to corneum and basal layer. (c, d) Intracytoplasmic vacuoles within peripheral blood neutrophil and monocyte represent “Jordans’ anomaly”.

3)Electron microscopic examination. Number of lipid droplets within the cytoplasm of corneocytes. Accumulation of abnormal lamellar granules lacking the normal lamellar content in the stratum granulosum/stratum corneum interface.

4) Sequencing analysis of *CGI-58* gene. A novel heterozygous 215T>C transition in the exon 3, that substitutes isoleucine for threonine at position 72 (Ile72Thr).

5) Distinct seasonal variation of ichthyosis. Ichthyosiform lesions were aggravated from spring and formed erythroderma throughout hot season, but ameliorated in winter.

6) Lipid analysis of scales taken from sunburn lesion as controls (white bar), patient’s lesions at aggravation and remission stages (black, shaded bars, respectively), showing positive correlation of increased TG levels with disease severity. Mean ± s.d. µg/ mg dry scale. FFA levels are invariably decreased in patient’s scales.

7) Topical application of l-menthol containing pasting resulted in local resolution of his ichthyosiform lesions.

8) Transient receptor potential M8 (TRPM8) was expressed in the normal skin. Menthol is an agonist of TRPM8, which is activated by low temperature below 25°C.

9) Skin water holding capacity ameliorated ichthyosiform lesions of DCS with 5%menthol treatment.

10) mRNA level of CGI-58 in cultured keratinocytes was up-regulated by menthol stimulation.

Our hypothesis

We consider that topical treatment with menthol is relevant to cold sensing in winter season, by which CGI58 expression may be reversed likely through TRPM8 stimulation in keratinocytes leading to improvement of ichthyosiform condition.

Conclusion

- The decrease of FA and resulting acylceramide deficiency in epidermal keratinocytes directly contribute to ichthyosiform phenotype of the present case with DCS.
- Topical treatment with menthol improved not only clinical findings but also skin water holding capacity.
- We speculate that temperature-dependent mechanism likely through TRPM8 may be involved in the pathophysiology of this specific patient.
- Our case gives a new piece of puzzle to elucidate the association between lipid metabolism pathway and thermo-regulation in keratinocytes.