Autosomal recessive congenital ichthyosis due to PNPLA1 mutation in a golden retriever–poodle cross-bred dog and the effect of topical therapy

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Introduction

Ichthyoses represent a genetically and phenotypically heterogeneous syndrome of abnormal epidermal cornification; they are classified into different subtypes based on clinical phenotypes, mode of inheritance and causative gene mutations. Recently, the umbrella term of autosomal recessive congenital ichthyosis (ARCI) was introduced to encompass the entities previously known as lamellar ichthyosis, congenital ichthyosiform erythroderma and harlequin ichthyosis. At this time, canine variants of ARCI have been characterized in the golden retriever, Jack Russell terrier and American bulldog breeds.

Similar to human ARCI, the clinical presentations, histopathological findings and genomic mutations of the canine syndrome vary with the genetic ethnicity/breed. In golden retriever dogs, the clinical phenotype is that of a nonepidermolytic ichthyosis characterized by generalized, small to large and white-to-grey scaling. Microscopic skin lesions include diffuse laminar to compact hyperkeratosis with absent-to-minimal epidermal hyperplasia, perinuclear vacuolation and a lack of dermal inflammation. Mutations in the PNPLA1 gene, encoding the patatin-like phospholipase domain-containing protein-1, have been shown to underlie ARCI in golden retrievers and rare human individuals. These mutations are suspected to contribute to defective lamellar granule function and/or formation, with the end result being a malformation of the intercellular stratum corneum lipid layer and an abnormal desquamation.

Accepted 30 March 2016

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In humans, the ideal treatment for ARCI would be to implement a treatment regimen, either topical and/or systemic, which would specifically correct the causative genetic defect. In dogs with ichthyoses, one review paper recommended symptomatic topical therapy using keratolytic agents and moisturizers/emollients as the treatment of choice for all variants of this syndrome. Regrettably, previous reports of PNPLA1-associated ARCI in golden retriever dogs did not provide information on treatment and outcome; therefore, the optimal management of this disease remains uncharacterized.

In this report we describe the partially successful treatment approach in a golden retriever and poodle crossbread dog (hereafter referred to as a “goldendoodle”) with ARCI due to a PNPLA1 mutation, using oral and topical fatty acids.

Case report

A six-month-old, intact female, second generation (F2) goldendoodle dog was referred to the NC State Veterinary Hospital for investigation of excessive generalized scaling. The owner had obtained the dog from a breeder when it was 6 weeks of age and abnormal severe scaling was already seen at that time (Figure 1). The sire, dam and five littermates were clinically normal and did not exhibit any visible scaling. Prior treatments of the affected dog with once or twice daily oral fish oil and coconut oil (unknown formulation), together with once weekly moisturizing shampoo (HyLyt, Bayer Animal Health; Shawnee, KS, USA) did not provide any visible benefit.

At initial presentation the dog exhibited a severe diffuse generalized scaling that was most prominent on the dorsal area of the abdomen and medial thighs (Figure 2a). Small and large, white scales, some with embedded hair shafts, were loosely adherent to the skin. White-to-tan scales were also prominent on the glabrous ventral abdomen and medial thighs (Figure 2b). Other abnormalities were not detected on physical examination.

Three punch skin biopsy samples were taken from the flank, ventral abdomen and caudal dorsum. Microscopic skin lesions revealed diffuse, laminated-to-compact hyperkeratosis with mild epidermal hyperplasia without dermal inflammation (Figure 3a). Occasional stratum granulosum keratinocytes had a single small perinuclear vacuole (Figure 3b).

Altogether, the history, clinical signs and microscopic findings led to the diagnosis of an ARCI variant resembling that seen in golden retrievers. Genetic testing (Optigen; Ithaca, NY, USA) performed with a venous blood sample confirmed, in this goldendoodle dog, the presence of an homozygotic insertion/deletion mutation in PNPLA1 identical to that seen in golden retrievers with ARCI.

The initial treatment protocol consisted of oral fatty acid supplementation (Efa-Z, Virbac; Carros, France; two pumps twice daily) and the addition of a humectant rinse (Humilac, Virbac) following bathing with the previously prescribed moisturizing shampoo (HyLyt) once weekly.

Two months later, the dog had shown a mild improvement in clinical signs: whereas the dorsal area still exhibited moderate to severe scaling (Figure 2c), there were few scales and mild skin wrinkling remaining on the glabrous area of the abdomen and medial thighs (Figure 2d). Weekly applications of a topical essential oil and fatty acid product (Dermoscent Essential 6 spot-on, LDCA; Castres, France) subsequently were initiated on the neck between the shoulders. Five months later, a further improvement in dorsal scaling was seen. Thirteen months after the initial presentation, the dog exhibited a marked improvement in clinical signs (Figure 2e and f) with only mild visible scaling remaining on the dorsum and lateral thighs. In one instance, the owner reported that scaling had worsened when topical medications had not been applied for 2.5 weeks, even though oral fatty acid supplementation was still given. After all topical therapies were resumed, skin lesions again improved. Furthermore, because the owner perceived that there was less scaling at spot-on application sites, compared to the other parts of the body, application sites were then rotated every week.

In order to determine if the humectant (Humilac) was of help for scaling management, this product was requested to be discontinued. Two months later, the owner reported that the skin lesions had not deteriorated further. At 18 months after the initial presentation, the disease was well controlled with twice daily oral fatty acid supplementation and once weekly moisturizing shampoo (HyLyt) followed by the topical essential oil and fatty acid combination product applied once weekly (Dermoscent).

Discussion

To the best of the authors’ knowledge, this is the first case report of ARCI due to PNPLA1 mutation in a goldendoodle dog. The mode of inheritance of ichthyosis with mutations of PNPLA1 in golden retriever dogs is autosomal recessive, with heterozygous carriers being asymptomatic. Based on the known
phenotypes of relatives of this goldendoodle dog, the review of a tentative pedigree also suggests an autosomal recessive mode of inheritance (Figure 4). Because purebred poodle dogs have not been reported to have any PNPLA1-associated ARCI, and because genetic testing identified the mutation of PNPLA1 previously found in golden retriever dogs, the trait was likely inherited from the golden retriever ancestors with the subject being a homozygote mutated second-generation goldendoodle dog. Genetic testing was not performed in either asymptomatic sire or dam (both first-generation goldendoodles), however, both dogs were presumed to be heterozygous carriers. Five unaffected littermates of this dog could have been either normal without mutations or heterozygous carriers for the trait.

Figure 2. Clinical response of skin lesions in a goldendoodle dog with autosomal recessive congenital ichthyosis (ARCI) before (a, b), after 2 months (c, d) and after 13 months (e, f) of treatment. At treatment onset, large scales exfoliated from the dorsum (a) and white-to-tan scales with wrinkling were prominent on the glabrous areas of ventral abdomen (b). Two months later, the dorsal skin still exhibited moderate-to-severe scaling (c) but there was some decrease in the severity of scaling on the glabrous area of the abdomen (d). Thirteen months after starting topical therapy scaling had improved markedly on the dorsum (e) and abdomen (f).

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A long-term combination treatment with oral fatty acid supplementation and topical therapy appeared beneficial in this case. It is presumed that the topical therapy was important for the management of ARCI in this case because: (i) there was deterioration of skin lesions after temporary discontinuation of topical essential oil and fatty acids; and (ii) the added application of topical therapies resulted in further clinical improvement. This topical essential oils and fatty acid combination (Dermoscent) was shown previously to significantly decrease transepidermal water loss in dogs with atopic dermatitis, which suggests its effect to be that of an emollient. Given that golden retriever dogs affected with ARCI have ultrastructural and fatty acid keratinocyte metabolism changes, suggestive of defective intracellular stratum corneum lipid formation, the application of high concentrations of topical fatty acids theoretically might be beneficial for improving clinical signs.

The clinical signs in this dog gradually improved over time. Because multiple products had been added to each other with time, it is difficult to determine which combination of treatment would be optimal for the management of this disease. The continued control of scaling after discontinuation of the humectant suggests that it is the fatty acids that were of benefit, perhaps because of their compensation of a putative defect in PNPLA1-induced glycerophospholipid metabolism caused by the PNPLA1 mutation. Why the abdominal skin became less scaly than the dorsum to which the topicals were applied remains unexplained.

In conclusion, to the best of the authors’ knowledge this is the first case report of ARCI due to a PNPLA1 mutation in a goldendoodle dog. Although long-term combination treatment with oral fatty acid supplementation and topical therapy appeared to be beneficial in this case, reports of further cases with ichthyosis treated in a similar way are necessary to determine which subset of ARCI is likely to benefit from this combination.

References
In this article we describe the management of an Golden Retriever crossbred with a Poodle (Goldendoodle) with ARCI due to a mutation in PNPLA1 (Patatin-like phospholipase domain containing 1).

**Étude clinique** – Un chien croisé Golden Retriever-caneche de la seconde génération, femelle entière de 6 mois, présentée pour un squamosis généralisé évoluant depuis l’âge de 6 semaines. L’histopathologie a montré une hyperkératosose diffuse, stratifiée à compacte avec des kératinocytes du stratum granulosum présentant occasionnellement une unique petite vacuole périnucléaire. Les tests génétiques ont révélé une mutation homozygote chez un chien croisé Golden Retriever-caneche avec ARCI due à une mutation de PNPLA1 (Patatin-like phospholipase domain containing 1).

**Conclusions et importance clinique** – À notre connaissance des auteurs, ceci est le premier cas d’ARCI avec mutation PNPLA1 homozygote chez un chien croisé golden retriever-caneche. L’association à long terme d’acides gras essentiels oraux et d’un traitement topique semble être efficace dans ce cas.

**Schlussfolgerungen und klinische Bedeutung** – Nach bestem Wissen der Autoren handelt es sich hierbei um den ersten Fall von ARCI mit einer homozygoten PNPLA1 Mutation in einem Golden Retriever/Pudelmischlingshund. Die Langzeitanwendung der Kombination von essentiellen Fettsäuren und einer topischen Therapie schien diesem Fall gut zu tun.

要約
背景 — 魚鱗症は遺伝的および表現的に多様な、異常な表皮角化を示す症候群である。ゴールデンデフォリーバー犬における常染色体劣性遺伝の先天性魚鱗症(ARCI)の臨床所見、病理組織学的所見および遺伝的原因はよく研究されているが、この疾患の最適な管理法は明らかにされていない。
目的 — この報告において、筆者らはPNPLA1(パラチジックホスピマーゼDドメイン含有)1変異に起因するARCIの、ゴールデンデフォリーバーとブーロールの交雑種犬(ゴールデンデフォリーバー)の管理における経口および外用脂肪酸の有益な効果を解説する。
症例報告 — 6か月齢、未断姦ステ、ゴールデンデフォリーバーとブーロールの第二世代交雑種が生後6か月から全般的塊の病歴を示した。病理組織学では、間葉細胞の核周に膵状核の小形の空胞を伴う、びまん性で異常な表皮角化が認められた。遺伝子検査ではPNPLA1遺伝子における插入/欠損ホモ接合変異を明らかとなった。通過の経口脂肪酸サプリメント、および1回の保満性シャンプーとその後の保満性シャンプーは、2か月後に軽度の改善のみを示した。週に1度の外用エッセンシャルオイルおよび脂肪酸製剤を追加した。初診から1か月後、イスに臨床症状において顕著な改善を示した。一時的な外用療法の中止で鱗屑は悪化したが、この治療の組み合わせを再開することで再び改善した。
結論および臨床的重要性 — 筆者らが示すところによれば、これはゴールデンデフォリーバーとブーロールの交雑種犬におけるPNPLA1ホモ接合変異のARCIの最初の症例報告である。長期的な経口脂肪酸および外用療法の組み合わせがこの症例では有益であったようである。

概要
背景 — 魚鱗症は遺伝性疾患、一種の表皮異常角化の多彩化表現综合征。金毛犬鉄素潜性遺伝先天性魚鱗症、雖然あるの臨床表現、組織病理学は遺伝子研究を研究したが、その遺伝的治療管理は明らかにされていない。
目的 — 这の報告中、一の金毛犬と貴賓犬は育飼義の交雑犬、金毛犬と貴賓犬がARCIを伴うPNPLA1変異を有するatori、報告するための口服と外用脂肪酸に対する管理試予の療法。
症例報告 — 6か月齢、雌性、金毛犬が貴賓犬を交雑交雑犬の新生犬、6か月齢時に出現した塊、組織病理学表現出弾性、異常な角化過形成、異常な表皮細胞が異常な細胞核が見出された hacropatellar。検査確認PNPLA1基質上存在する純合型基質/嵌合型変異。毎日口服補充脂肪酸と保湿剤を洗う、洗う毎に用いて保湿香油を、2か月後に軽度改善、毎日添加外用と脂肪酸製剤、13か月後に临床症状が改善、暂时的に停止外用薬用皮膚剤、重複使用外用薬用皮膚剤再び改善。
総合と臨床意義 — 据作者所知、这是第一例有关纯合PNPLA1突变导致ARCI的报道。报道动物为金毛巡回犬和贵宾犬交配所生的杂交犬。生理口服脂肪酸和外部治疗相结合，在此病例中表现出一定效果。