Ichthyosis and eye care
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Importance of eye care in ichthyosis

The primary aim of eye care for adults and children with ichthyosis is to maintain moisture, integrity and clarity of the cornea (transparent part of the eye) and surface of the eye. There is a high risk of the cornea becoming dry and developing an epithelial defect (a breach in its protective surface) that may result in an infection of the cornea. Infections of the cornea may result in a scar that reduces the clarity of the eye, or at worst a perforation of the cornea. The surface of the cornea requires a moist tear-film on its surface in order to provide a *clearer-than-glass* window for vision. Blinking is a natural method of ensuring this moist tear-film is smoothly spread and maintained over the entire surface of the eye. Any redness of the eye should raise suspicion of dryness, particularly if blink or normal full eyelid closure is incomplete, as is often seen in ichthyosis. In addition, the first 8-9 years of life also represents the critical period for visual development. During this period, the brain requires the clearest image to be transmitted through the eye in order for the visual pathway (circuit from eye to brain) to develop into a *high-definition* visual system. Any prolonged blurring of vision, due to a scarred or hazy cornea or any uncorrected refractive error (not wearing glasses for long-sightedness, astigmatism or even short-sightedness) during this period will result in vision that will remain blurred throughout one's adult life. Thankfully, with the involvement of an ophthalmologist (eye specialist) this can be identified and treated, or better still, avoided. It is therefore rare nowadays to occur. In adults, a contrary response to evaporative-type dry eye is *reflex tearing*. This may be considered as the body's response in attempting to lubricate the drying surface of the eye. Individuals who experience this may not have significant symptoms of ocular discomfort or redness of the eye. Reflex tearing may occur outdoors in cold and windy weather or in a dry, air-conditioned environment. The eyes may remain *white* in appearance, or in extreme conditions become *pink*. However, they seldom become red or cause pain.

Preservative-free ocular lubrication.

If incomplete blink or eyelid closure exists, then regular eye lubrication with artificial tears is essential. Preservatives are a legal requirement for eye drops in multi-dose containers and may be necessary for stabilization of eye drops. However, they often

act in a non-specific manner as detergents or for unknown reasons occasionally cause side-effects on the surface of the eye such as redness, inflammation, irritation and discomfort. Prolonged use of certain preservatives (i.e. Benzalkonium chloride, BAK) on the eye may cause long-term surface scarring due to toxicity. *Preservative-free* artificial tear eye drops are strongly recommended for patients who require frequent eye drops.

Examples of lubricants to use include 0.5–1% carboxymethylcellulose, hyaluronic acid (HA) or carmellose-sodium, and petroleum ointment at night if nocturnal lagophthalmos (incomplete eye closure when sleeping) exists. These are available under many brand names. As a principle, eye drops are used in the day and an ointment at night. If blink or eyelid closure is incomplete, then frequency of drops required may be intensive (even every 30 minutes or less). This regime will be guided by your ophthalmologist (specialist eye doctor). In certain situations, ointment may be necessary during the day to ensure a moist eye surface and *white-eye* is maintained.

General measures

Room humidifiers help maintain a moist environment for dry eyes. A meta-analysis including 7 trials, aimed to evaluate the effect of a moisture chamber compared with lubrication for corneal protection in critically ill patients concluded the use of moisture chambers is associated with more effective corneal protection compared with lubrication alone but no statistically significant difference between the use of moisture chambers and lubricating ointments. (Zhou Y et al. 2014) Intensive ointments however, can significantly blur vision and are not practical as a permanent, long-term option.

Wrap-around glasses for dry eyes are an excellent method of increasing humidity around the surface of the eye, in order to create a moisture chamber effect. These are an ideal style of spectacle frame when spectacle-wear is necessary, for adults and children with ichthyosis. In addition, they are an excellent choice of frame for sunglasses.

Eyelid moisturising and stretching

Conservative treatment with intensive ocular lubricants, eyelid emollients and massage can result in improvement of eyelid ectropion and to some degree *retraction* of the eyelid. Retraction of the eyelid describes how in addition to the eyelid being turned out (ectropion), it is usually *pulled* down (or, *retracted*) due to tight skin. The upper eyelid may also be retracted (or pulled up), preventing eyelid closure during blink, or when asleep.

Regular stretching of the eyelid skin and application of eyelid emollients can avoid the need for eyelid surgery in mild forms of congenital ichthyosis. Resolution of ectropion of all 4 eyelids (that was more obvious during enforced eyelid closure) was reported in a premature male baby with frequent application of eyelid ointment and spontaneous desquamation. (Menke TB et al. 2006) Severe ectropion of all 4 eyelids in a child with Lamellar ichthyosis (LI) was reported to have reduced with preservation of the ocular surface using regular lubricant drops, vitamin A ointment and intermittent topical antibiotic therapy. No surgery was required during the reported follow-up period. (Elshtewi M and Arche DB 1991)

Another example has been reported (Oestreicher JH and Nelson CC 1990) in 2 infants with LI, aged 2 and 6 weeks, with ectropion and retraction of all 4 eyelids causing signs of drying of the cornea. Ectropion improved within 3 months with

conservative treatment of ocular lubricants, eyelid emollients and massage. Based upon the photographs in their report, eyelid retraction still existed as would have incomplete blink closure, however this required lubricants only within the follow-up period reported. *Some* improvement with conservative management including humidified air and emulsifying agents was reported in another case. (Leung PC and Ma GF 1981) However, the child still required skin grafts to all 4 eyelids and repeat grafts 18-months later due to recurrence.
Evidence does suggest, therefore, that consistent and life-long vertical lid massage and stretching may help delay progression or recurrence of ectropion due to retraction of the eyelid.

Meibomian gland dysfunction
Meibomian gland dysfunction (MGD) is likely to occur in most cases of ichthyosis even if not specifically documented. The meibomian glands exist on the eyelid margin and normally produce the oily layer of the tear film. Absence of the normal oily layer of the tear film causes the tears to evaporate too quickly. This contributes to evaporative-type dry eye further and to symptoms of photophobia (intolerance to bright lights) and discomfort, soreness or itchiness of the eyes. This can increase the likelihood of the presence of corneal punctate staining (evidence of drying of the cornea when examined by an eye specialist) and even corneal scarring. At best, MGD may simply increase symptoms of *reflex tearing* without any eye discomfort.
Simple treatment options for MGD involves a daily regime of expressing the oily tears from the glands using hot compresses. A face cloth, or cotton pads, soaked in hot (not boiling) water may be used. On closed eyes, hold the hot cloth onto the eyelids. Wet the cloth again with hot water and keep applying the compress for at least five minutes. This can be carried out daily, perhaps in the evening. Products known as ‘heat bags’ that are specifically designed for this condition may be easier to use with more prolonged heat. These bags make it easier to direct the heat and are much more effective than a hot cloth. Examples include the MGDRx EyeBag®, the Eyevolve Mask® or the OPTASE™ Heat Mask.
There is also evidence of a benefit in maintaining optimum levels of omega-3 essential fatty acids in the diet for improving MGD. (Macsai MS 2008) It is also suggested that individuals should return to a more desirable omega-6 to omega-3 ratio of 4:1 rather than the ratio of 15–18:1 provided by current Western diets. This entails decreasing the intake of omega-6 fatty acids from vegetable oils and to increase the intake of omega-3 fatty acids by using oils rich in omega-3.
Experimental studies suggest that dietary supplementation of omega-3 fatty acids modifies inflammatory and immune reactions. (Macsai MS 2008) More carefully designed and controlled clinical trials to determine the real benefit of omega-3 fatty acids in MGD and evaporative-type dry eye are still needed, but the current medical consensus recommends a trend towards this diet for dry eye patients, if given a preference.

Topical cutaneous N-acetylcysteine emollient
Topical N-acetylcysteine has anti-proliferative effects on keratinocytes both in-vitro and in-vivo. It may have a role in the management of eyelid ectropion in children with Lamellar ichthyosis. Bassoti et al (Bassoti A et al 2011) reported the use of topical 10% N-acetylcysteine emulsion prepared in urea 5% in 5 children with LI.
The emollient was applied twice daily for 6 weeks, followed by a daily maintenance application including the eyelids without any irritation (provided the skin had no fissures). With up to 4-years follow-up, they observed a significant improvement in all

treated areas after 4 months of maintenance application. Only two patients showed mild adverse effects such as itchiness (resolving after a few days in one patient), and light burning and irritation that regressed a few days after tapering N-acetylcysteine to 5% on the facial application.
Gicquel et al (Gicquel JJ et al. 2005) reported what they described to be complete resolution of ectropion with adjunctive topical N-acetylcysteine in an 8-week-old boy with LI and severe bilateral ectropion. Bilateral sight-threatening
upper eyelid ectropion persisted whilst receiving initial treatment with only oral acitretin for 1 month until N-acetylcysteine was added, thus avoiding the need for surgery.
Deffenbacher (Deffenbacher B 2013) reported the initial use of 10% N-acetylcysteine and 5% urea in a newborn with LI, who initially failed to improve with standard treatment of topical emollients. After 3 days of once daily use, the mother noted some decreased thickness of scales, but also noted increased skin sensitivity and erythema. The 10% cream was discontinued. Two-days after discontinuation of the topical treatment, it was noted that the skin was less tight and scales were less thick than the month before. A less-potent mixture with 5% N-acetylcysteine and 5% urea compounded in a moisturising skin cream in addition to the continued frequent use of emollients was commenced. One month later, the infant was able to close his eyes whilst sleeping and had significantly improved with only mild erythema. At 7 and 12-months, continued improvement was observed in scaling and eyelid involvement.

Topical retinoids to treat eyelid ectropion
Systemic retinoids modulate keratinocyte differentiation and proliferation with only a modest therapeutic effect in eyelid ectropion or retraction due to ichthyosis (Diaz LZ et al. 2013). Tazarotene, a topical retinoid, works via binding of retinoic acid receptors in the skin. The beneficial use of tazarotene in congenital ichthyosis has been reported (Hofmann B et al 1999, Stege H et al. 1998, Marulli GC et al. 2003, Kundu RV et al 2006). Craiglow et al (Craiglow BG et al. 2013) reported the use of topical tazarotene cream, 0.1%, applied once daily to the face and eyelids in a 77-year old female with autosomal recessive ichthyosis and bilateral lower eyelid cicatricial ectropion. A rapid improvement within 2-weeks was observed and reported at 12 and 30-months of treatment. In their report, the authors also mentioned a 45-year-old man with severe LI and symptomatic ectropion who was reluctant to take oral retinoids and whose ectropion and tearing significantly improved with topical retinoid and later tazarotene cream, applied to the lower eyelids.

Surgical treatments
Patients with chronic corneal involvement or persistent corneal dryness require specialist eye care. Severe or persistent ectropion requires correction and this may involve increasing the amount of eyelid skin available for eyelid closure. For the best outcomes, an experienced ophthalmic plastic surgeon (or oculoplastic surgeon) should be involved.

Eyelid skin grafting
Eyelid skin grafting is generally undertaken where symptomatic corneal exposure or watering persists despite adequate conservative skin treatments. It should also ideally be undertaken before scarring of the ocular surface occurs. Skin grafts are the most commonly reported surgical intervention for ichthyosis ectropion. The successful use of both full-thickness and split-thickness autologous skin grafts have

been reported in correcting either eyelid ectropion, or retraction. Harvest sights for full-thickness grafts include the upper arm, behind the ear, collar bone region, thigh, groin, and even penile foreskin. Regardless of harvest site, repeat surgery due to skin graft contracture is often necessary. In one reported article, 4 patients required 19 surgical graft procedures, 10 of which were to upper eyelids involving grafts harvested from inner arm, behind the ear, the collar bone region and groin sites. Split-thickness skin grafts in a 25-year old has also been reported. Successful use of behind-the-ear and thigh full-thickness skin grafts have also been reported in 6-week and 6-month old babies, respectively, with Harlequin ichthyosis.

Oral buccal mucous membrane autogenous graft

Based upon the observation that in long-standing eyelid ectropion, keratinizing squamous metaplasia occurs in the tarsal conjunctiva (transformation of the inner moist lining of the eyelid to become a skin-like surface), in 2001, Soparkar and Patrinely (Soparkar DN and Patrinely JR 2001) wrote a letter describing and recommending the use of oral buccal mucous membrane (the moist inner lining of the cheek) in preference to skin for grafts of 1.5 cm or less of vertical height. This avoids delayed-healing donor-sites as oral mucosa is unaffected by ichthyosis. The authors did not report any specific cases in their letter but reported that they have used this approach for many years and showed photographs of an 8 year-old boy, 2 months and 2 years post upper and lower grafting, respectively. Once implanted into the eyelid, mucous membrane grafts rapidly keratinize (become like skin) with little desquamation or significant contraction. Nayak et al (Nayak S et al. 2011) have also reported the use of oral mucosal grafts as a skin substitute in a 26-year old female with LI and ectropion of all 4 eyelids. Left upper and lower eyelid defects were grafted from the left cheek and 4-months later, right eyelids from the right cheek. In the absence of available autologous skin, where non-surgical methods have proven in-effective, oral buccal mucous membrane autografts are a useful source of tissue to expand the eyelid skin layer.

Hyaluronic acid gel filler

In 2009, Taban et al (Taban M et al. 2009) reported their early experience using hyaluronic acid gel fillers as a nonsurgical alternative in the management of congenital eyelid malpositions including eyelid retraction, ectropion and other eyelid disorders. Filler helps improve eyelid position by tissue-expansion and reinforcement to improve eyelid closure, with faster recovery and fewer complications in comparison to traditional surgical procedures. Five patients treated demonstrated significant improvement of eyelid position and degree of corneal dessication with a mean improvement in the gap of incomplete eyelid closure of 4.5 mm (range, 2–7 mm) using an average of 0.5 ml hyaluronic acid gel per eyelid. Complications were minor, including transient swelling and bruising at the sites of injection.

In 2015, my team (Litwin AS et al. 2015) reported the use of this technique in 3 boys (4-months to 3-years of age) with LI and sight-threatening eyelid retraction and cicatricial ectropion of all 4 eyelids. In 2 cases treated by myself, Restylane-Lidocaine® (Galderma, UK) 1 mL per eyelid was used successfully with resolution or good improvement of lagophthalmos, corneal exposure and visual acuity and no repeat eyelid procedures required after 7 and 18 months, respectively. In the third, less successful case treated in Leeds, Restylane SubQ®(Galderma, UK) was used. However, SubQ® is not an ideal choice for use in the eyelid as it contains 1,000

molecules per 1ml, in comparison to 100,000 molecules per 1 ml for Restylane Lidocaine®, making it significantly denser and more viscous. It is better intended for deep subcutaneous or pre-periosteal injection to allow more extensive facial volume augmentation and structural support. This patient underwent repeat injections 5 and 12 months later, finally requiring skin grafts.
The technique for hyaluronic acid injections is similar to that described by Taban et al (Taban M et al. 2009). Injections can be performed under general anaesthesia for children at the same time as an examination. It can be an effective, repeatable method of eyelid expansion in ichthyosis that can act as a good temporising method, often delaying the need for more invasive surgical procedures. It can give rise to the appearance of fullness of the eyelid. It should however, only be undertaken by those experienced with fillers in the eyelid region.

Conclusion

This article provides advice and evidence for current options available for the eye care of patients with ichthyosis. It may also prove useful when discussing options available for your child or yourself with your specialist team of doctors. Simple measures such as humidifiers, wrap-around glasses, regular vision checks until the age of 9-years of age, preservative-free lubricants, eyelid emollients and stretching and MGD treatment are essential. Newer options such as topical N-acetylcysteine emollient and topical retinoids may be discussed with your dermatologist. When faced with the prospect of surgery, options such as buccal membrane grafts and eyelid filler may also be considered as alternatives to skin grafts, at least in the first instance. Life long eye care is often required for dry eyes. The currently available options outlined above are applicable to both children and adults.

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