Harlequin Ichthyosis

A Review of Clinical and Molecular Findings in 45 Cases

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Objective: To assess the clinical outcomes of 45 cases of harlequin ichthyosis and review the underlying ABCA12 gene mutations in these patients.

Design: Multicenter, retrospective, questionnaire-based survey.

Setting: Dermatology research institute.

Participants: Patients with harlequin ichthyosis for whom we had performed ABCA12 mutation analysis.

Main Outcome Measures: Referring physicians were asked to complete a questionnaire using the patients’ notes, detailing the clinical outcome of the affected child. In each case, the causative ABCA12 mutation was identified using standard polymerase chain reaction and sequencing techniques.

Results: Of the 45 cases, the ages of the survivors ranged from 10 months to 25 years, with an overall survival rate of 56%. Death usually occurred in the first 3 months and was attributed to sepsis and/or respiratory failure in 75% of cases. The early introduction of oral retinoids may improve survival, since 83% of those treated survived, whereas 76% who were not given retinoids died. Recurrent skin infections in infancy affected one-third of patients. Problems maintaining weight affected 44%. Three children developed an inflammatory arthritis, and developmental delay was reported in 32%. Mutation analysis revealed that 52% of survivors had compound heterozygous mutations, whereas all deaths were associated with homozygous mutations.

Conclusions: Harlequin ichthyosis should be regarded as a severe chronic disease that is not invariably fatal. With improved neonatal care and probably the early introduction of oral retinoids, the number of survivors is increasing. Compound heterozygotes appear to have a survival advantage.


HARLEQUIN ICHTHYOSIS (HI) (OMIM 242500) is a rare, severe form of congenital ichthyosis, which may be fatal. The neonate is encased in an “armor” of thick scale plates separated by deep fissures. There is bilateral ectropion and eclabium, and the nose and ears are flattened and appear rudimentary. Constricting bands around the extremities can restrict movement and cause digital necrosis. As the skin barrier is severely compromised, neonates are more prone to sepsis, dehydration, and impaired thermoregulation. Treatment with oral retinoids encourages shedding of the grossly thickened skin.1 Babies who survive into infancy and beyond develop skin changes resembling severe nonbullous congenital ichthyosiform erythroderma (NBCIE).2

Recessive mutations in the gene encoding the adenosine triphosphate (ATP)-binding cassette (ABC) transporter protein ABCA12 (NCBI Entrez Gene 26154), localized to the lamellar granules of upper epidermal keratinocytes, cause HI.3,4 Electron microscopy of lamellar granules in HI skin has shown that they are absent, abnormally shaped, or reduced in number and that no intercellular lamellae are present.3 It is postulated that ABCA12 transports glucosylceramide into the lamellar granules, where it is then processed and secreted into the stratum corneum extracellular space to form lipid lamellae.4 Expression of markers of late epidermal differentiation is highly dysregulated in HI skin, suggesting that ABCA12 may have a key role in keratinocyte differentiation.6 Reports of HI to date

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have focused on the infant, and there is relatively little in the literature about the outcome of older children and adult survivors. We have conducted a review of the clinical outcomes of HI cases referred to our center for ABCA12 mutation analysis.

**METHODS**

Fifty-six referring physicians were identified from our database and with the consent of their patient(s) were asked to complete a “detailed” systems-based questionnaire. Ethical approval was obtained from the local research ethics committee. We have previously briefly reported the clinical outcomes of 12 babies with HI. These “brief” questionnaire responses were used in this review if the child was deceased at the time of the original study or if no further information was available.

Primer design and polymerase chain reaction (PCR) conditions were the same as those described elsewhere, with the exception that a 15-µL reaction volume was used. The PCR products were purified and sequenced as described previously.

**RESULTS**

**DEMOGRAPHIC AND MORTALITY DATA**

Clinical data were obtained for 45 patients (eTable; http://www.archdermatol.com). This consisted of 33 completed detailed questionnaires and 12 brief questionnaires. In total, there were 25 survivors (56%) and 20 deaths (44%). The mean gestational age at birth was 35 weeks (range, 30 to 39 weeks). Sex was reported for 43 patients (20 male and 23 female). The ages of survivors ranged from 10 months to 25 years. The children came from several different ethnic groups (eTable). The high incidence of Pakistani and Arab families probably reflects the practice of consanguinity in these groups. Indeed, 38% of all parents were first cousins and 29% were unrelated, and in 33% the information was not available. However, 86% of the latter showed homozygous mutations (the same mutation on both ABCA12 alleles) suggestive of consanguinity.

The mortality rate was 44% (20 of 45 patients), with the age of death ranging from day 1 to day 52. Of the 20 deaths, 15 (75%) were caused by fulminant sepsis (n = 5 [25%]), respiratory failure (n = 5 [25%]) or a combination of the 2 (n = 5 [25%]). There was 1 stillbirth, and in 4 cases the cause of death was unknown.

**PRENATAL TESTING**

Prenatal ultrasonography results were available for 6 cases, all with previously affected children, from 22 weeks onwards. Routine fetal anomaly scans used in the early stages of pregnancy were not included. In 3 cases, features suggestive of HI were seen, including rudimentary ears, flexion contractures at the knees, and dense floating particles in the amniotic fluid. In the last case, previously described by Vohra et al, an open mouth with a protruding tongue and echogenic amniotic fluid were noted.

**TREATMENT WITH RETINOIDS**

Of 45 babies, an oral retinoid drug was given to 24, and 20 (83%) survived. Among the 20 survivors, treatment was started within the first 3 days of life in 9 babies (45%) and between days 4 and 7 in 7 babies (35%) and was deferred until 2 years and 11 months in another case. One baby received a retinoid as a neonate, and in 2 cases the start date was unknown. Four children died despite receiving a retinoid. Within this group, treatment was started by day 3 in 3 babies (75%). Twenty-one babies did not receive a retinoid, and within this group, 16 (76%) died. Of these 16 deaths, 10 (63%) occurred by day 3.

With the exception of 2 patients treated with etretinate and 2 with isotretinoin, the remainder (n = 20) all received acitretin. The retinoid dose ranged from 0.5 to 2.5 mg/kg (eTable). This was constant in 18 cases, but in 4 the dose was adjusted according to response and tolerability. In 2 cases the dose was not stated. Among the 20 survivors, 14 (70%) received 1 course of treatment, 4 (20%) had 2 separate courses, and 2 (10%) received more than 2 courses. Continuous treatment was given for up to 6 months in 13 cases, up to 1 year in 3 cases, up to 2 years in 3 cases, and from 3 to 7 years in 4 further cases. The length of treatment was unknown for 4 patients.

**CLINICAL FINDINGS ASSOCIATED WITH HI**

**Skin Abnormalities**

**At Birth.** All babies had the typical harlequin appearance at birth, with truncal plates with fissuring, bilateral ectropion, and eclabium. Hyperkeratotic skin resulted in anteverted nares and ears lacking retroaural folds. Of 45 children, 5 developed autoamputation of digits due to constricting skin bands. One child who subsequently died underwent a fasciotomy for limb swelling due to constriction.

**Infancy and Beyond.** Babies who survived into infancy had a severe ichthyosiform erythroderma. Of 25 survivors, 13 (52%) had a palmoplantar keratoderma. Plantar changes were associated with pain on weight bearing and delay in walking. Recurrent skin infections were reported in “early childhood” and affected 8 of 25 patients. Among these 8 patients, cultured organisms included methicillin-resistant *Staphylococcus aureus* (n = 5), *Staphylococcus aureus* (n = 4), *Streptococcus pyogenes* (n = 4), and *Klebsiella* (n = 2). Both heat and cold intolerance were reported in 9 of the 25 survivors (36%), as was reduced sweating (n = 7 [28%]). Pruritus affected 11 of these 25 patients (44%). Photosensitivity was reported in 1 case, and widespread, pigmented macules were observed in another patient. One patient had several episodes of widespread sterile pustulation attributed to generalized pustular psoriasis, associated with nail shedding.

**Hair and Nail Problems**

Generalized poor hair growth affected 16 of the 25 survivors (64%). In 1 patient, this was limited to the pari-
et al and occipital scalp, and in another there was regression of all the hair margins. One child aged 7 years had no scalp hair. Nail deformities were observed in 16 of the 25 survivors (64%). Among these 16 patients, 11 (69%) had abnormally shaped or small nails, 8 (50%) had thickened nails, and in 1 case, surgical amputation of the terminal phalanges of 2 fingers was required because of onychogryphosis.

**Ophthalmological Problems**

Persistent ectropion was found in 16 of the 25 survivors (64%) and was corrected in 5 patients. Among the 25 survivors, epiphora was reported in 12 (48%), recurrent conjunctivitis in 5 (20%), exposure keratitis in 3 (12%), squint in 2 (8%), and nystagmus in 4 (16%). The latter was noted in 1 child who survived a cardiac arrest and was unexplained in the other 3 cases. Of the 25 patients, 1 each had corneal scarring and corneal perforation, 2 had punctate corneal erosions, and 1 developed cataracts while receiving concomitant corticosteroid therapy and another while receiving acitretin.

**Gastrointestinal Problems**

Among the 25 survivors, problems maintaining weight despite high-calorie supplements were reported in 11 (44%). Two children required nasogastric feeding tubes in infancy, and 1 had overnight supplementary feeding via a gastrostomy tube, performed intermittently until the age of 6 years. This is probably an underestimate because we did not specifically enquire about the use of feeding tubes. Chronic constipation requiring regular laxatives affected 11 of the 25 children (28%). Three children were treated for gastroesophageal reflux. Finally, vitamin D deficiency causing rickets and osteomalacia was reported in 3 patients, and 1 patient developed scurvy during a 3-year period when the child was out of the country and lost to follow-up.

**Height and Weight Abnormalities**

Height and weight were both below average, lying between the 0.4th and 25th percentiles, resulting in most children being short and thin for their age. One child receives regular somatotropin injections (started at age 9 years and currently ongoing) to promote growth.

**Locomotor Problems**

Of the 25 survivors, 7 reported joint pain, most commonly affecting the knees. In 3 cases this was associated with an inflammatory arthritis. One case was previously reported by Clement et al. The patient had juvenile idiopathic arthritis and required systemic treatment with methotrexate and the anti–tumor necrosis factor drug etanercept before having bilateral hip arthroplasties at age 17 years. The second case developed an intermittent, painful swollen right knee and ankles and was treated with nonsteroidal anti-inflammatory drugs for 1 year and currently has nighttime splinting to prevent joint contractures. The final patient was noted to have erosions on a joint radiograph, but details of further management were not available. None of the patients were being treated with retinoids at the time of reporting the joint pain. In addition, 4 of the 25 survivors (16%) required surgical correction of contractures.

**Neurological Problems**

Developmental delay was reported in 8 of the 25 survivors (32%). This included delayed developmental milestones and fine and gross motor skills. Four children living in the United Kingdom required speech and language therapy. Of these, 1 child had cerebral palsy and 3 children showed significant developmental delay.

**Respiratory Problems**

Respiratory problems were most common in the neonatal and early infancy periods and were a major cause of death in neonates. Of the 25 children who survived, 3 (12%) required mechanical ventilation and 1 had intermittent episodes of oxygen desaturation in the first 2 weeks. Another 3 patients (12%) had respiratory failure secondary to respiratory syncytial virus, and 1 patient developed pulmonary interstitial fibrosis.

**Ear, Nose, and Throat Problems**

Deafness was reported in 1 of 25 survivors. Six children experienced recurrent blockage of the external auditory canal and required regular microsuctioning to remove skin debris.

**Urological Problems**

Surgical correction of phimosis in 1 patient and urinary incontinence due to an unstable bladder in another patient were reported. One child underwent circumcision without any problems.

**Biochemical Problems**

Hypernatremia, hypocalcemia, and hypoglycemia were reported separately in 3 of 25 patients in early infancy.

**Miscellaneous Problems**

Hepatosplenomegaly attributed to infection was reported in 1 patient. In another case, hepatosplenomegaly was associated with lymphadenopathy, bone marrow fibrosis, and pancytopenia. Histopathologic examination following splenectomy revealed splenic granulomas. Severe anemia requiring blood transfusion was reported in 3 of 25 cases.

**EDUCATIONAL DEVELOPMENT AND AFFECTED SIBLINGS**

Of the 17 school-aged children, 2 were in higher education, 9 attended a mainstream school, 2 attended a school for children with special needs, and 1, who lived...
outside the United Kingdom, did not attend school; details were unavailable for 3 children. In the United Kingdom, many children (55%) needed a statement of special educational needs. This is the provision of additional help for children who face difficulties in their ability to learn owing to their disease.

Differences in phenotype within families (3 sibling-pair survivors) included cerebral palsy in the younger child of one pair and significant developmental delay in the younger sibling of another pair.

### MUTATION ANALYSIS

ABCA12 mutations were identified in 38 of 45 patients. In the remaining 7, no mutation was found in either allele by standard PCR and sequencing (n = 3), DNA was unavailable (n = 2), or the analysis was performed elsewhere (n = 2). Patients with mutations were classified as homozygous if both alleles carried the same mutation (n = 27) or compound heterozygous, indicating that different mutations were seen on each allele (n = 11). All the deaths were associated with homozygous mutations. Among the mutations found in 21 survivors, 11 (52%) were compound heterozygous and 10 (48%) were homozygous.

### COMMENT

Harlequin ichthyosis is a rare disease, affecting all ethnic groups, that is associated with substantial morbidity and mortality. Previous reports have shown that many babies die soon after birth, but in our series the survival rate is higher than 50%. Reasons may include greater awareness of the condition, improved quality of care, and possibly early treatment with oral retinoids. In the retinoid-treated group, 20 of 24 patients (83%) survived compared with a 76% mortality rate in the untreated group (16 of 21 patients died). More than half of these deaths (10 of 16 [63%]) occurred in the first 3 days of life. However, only 45% of survivors received a retinoid within this time. This suggests that many of these early deaths may have happened irrespective of treatment with a retinoid. In some cases it may have been decided that palliative care only was more appropriate. A previous study recommended that the retinoid dose can usually be reduced and after 6 months therapy input may be needed to treat digital contractures or necrosis. Baseline biochemical and hematological tests should be carried out and abnormalities corrected. The retinoid dose can usually be reduced and after 6 months should be guided by clinical response.

Survivors will have a life-long skin disease that resembles NBCIE. The mechanism behind this phenotypic recovery remains unclear. Yanagi et al recently demonstrated disrupted keratinocyte differentiation in neonatal epidermis and primary-culture keratinocytes from an HI mouse model. With maturation, however, both the skin graft and subcultured HI keratinocytes regained normal differentiation, suggesting that this may contribute to the improvement in an HI survivor’s skin. Patients will still require frequent maintenance application of emollients, intermittent courses of oral retinoids in some cases, and protection from extremes of temperature. Vitamin D supplements will be required if skin exposure to sunshine is restricted. Patient support groups such as the Foundation for Ichthyosis & Related Skin Types (FIRST) (United States) and the Ichthyosis Support Group (United Kingdom) provide valuable help to families.

Preservation of visual function is crucial in survivors. Persistent ectropion is a frequent complication, and in this study 20% underwent surgical correction. The lack of intact donor skin for grafting makes this more challenging in HI. Full-thickness autografts from the thigh and posterior auricular skin have been described in HI as well as 1 case using engineered human skin. The long-term outcome of surgery in these cases is not known, but we report 1 case of epiphora postoperatively. Ectropion frequently recurs following surgical correction. An alternative approach is topical periocular retinoid treatment.

Early input from a dietician is necessary, since infants may have difficulty sucking because the jaw is splinted by thick scale, necessitating nasogastric feeding. Breastfeeding should be encouraged, particularly to promote parental bonding. Young children may need feeding via gastrostomy to maintain their calorific intake, whereas older children and adults are more likely to comply with high-calorie dietary supplements. To our knowledge, this is the first report of HI associated with rickets, although this has previously been reported in children with ichthyosiform dermatoses. Possible mechanisms for this include defective vitamin D synthesis in

kg/d. Serum lipids and liver function tests should be performed at baseline, 1 month after initiation of treatment, and every 3 months thereafter. Symptoms suggestive of skeletal toxicity should be promptly investigated, particularly in those children receiving doses greater than 1.0 mg/kg/d.

Management of HI in the neonate is largely supportive and involves the input of a multidisciplinary team. Emollients and the early introduction of an oral retinoid at an initial dose of 1 mg/kg/d encourage shedding of the thick “armor like” plates. It is important to keep invasive procedures to a minimum and to be vigilant for signs of sepsis to avoid skin infection. An ophthalmologist should be involved at an early stage to minimize complications caused by the ectropion and ear, nose, and throat specialists for aural toilet to remove debris from the ears. Plastic surgery input may be needed to treat digital contractures or necrosis. Baseline biochemical and hematological tests should be carried out and abnormalities corrected. The retinoid dose can usually be reduced and after 6 months should be guided by clinical response.

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the diseased epidermis and avoidance of exposure to UV radiation due to the disease.21

Juvenile idiopathic arthritis is a rare inflammatory arthritis. In addition to the 3 cases reported herein, another patient with HI aged 6 years is described in the literature who developed rheumatoid factor–positive polyarthritis.22 The coexistence of these 2 rare conditions suggests a common underlying etiology that is not yet understood.

Motor developmental delay was reported in almost one-third of the cases. Digital contractures and autoamputated fingertips can affect fine and gross motor skills, and thickened, fissured plantar skin may be painful and delay walking. Many of the children have frequent hospital admissions in infancy and, because of their disease, may also have fewer interactions with other children and adults, which affects their speech, language, and social skills.

The cause of death in HI is often speculative, since post-mortem examinations are not usually conducted. Review of the mortality data shows that respiratory failure causes death as commonly as sepsis. This may simply arise because the thickened skin restricts chest wall movements or makes breathing too painful, resulting in poor pulmonary ventilation. Opiate analgesia is given in the neonatal period to relieve this pain but may itself cause respiratory depression. Rajamani et al23 reported that aspiration of amniotic fluid rich in epithelial cells might have contributed to the development of pulmonary disease in a child with congenital ichthyosis, which is also plausible in HI. Furthermore, ABCA12 is also expressed in the lungs, testis, and placenta.7 ABCA3 aids lipid secretion from type II alveolar cells via lamellar bodies.24 Ultrastructural analysis of these cells in an HI mouse model has shown that lamellar body–like organelles lack the normal lamellar structure compared with wild-type mice, suggesting that ABCA12 protein may be involved in generating the lipid component of pulmonary surfactant.25 This would support our observation of a higher incidence of respiratory-related deaths in HI.

Mortality was associated with homozygous mutations in this study. Unpublished work (2010) by our group shows that some babies with compound heterozygous mutations also die but are in the minority. The coexistence of other serious recessive diseases may be one explanation. However, the nature of the ABCA12 mutation and its location within the protein may also affect the severity of the disease. Homozygous missense mutations in ABCA12 are known to cause type 2 lamellar ichthyosis in a subgroup of patients from Africa,7 as well as being a major cause of NBCIE.26 Both type 2 lamellar ichthyosis and NBCIE have a much milder phenotype than HI, in which most mutations are homozygous or compound heterozygous deletions or truncations. ABCA12 mutations in type 2 lamellar ichthyosis have been found exclusively in the first nucleotide-binding fold and in NBCIE have been reported in the extracellular domain and second nucleotide-binding fold. Akiyama et al27 reported a child with HI of moderate clinical severity who had a maternal deletion mutation of a highly conserved residue in exon 28 and a de novo missense mutation in exon 10, corresponding to the first nucleotide-binding fold and cytoplasmic domain, respectively. They argued that while the missense mutation would not be expected to significantly affect the function of the protein, in combination with the deletion mutation, the HI phenotype still appears but is of reduced clinical severity. In our series, 2 missense mutations were identified, namely V1089F in exon 23 combined with a splice site mutation in exon 33 in one patient, and G1179R (homozygous) in exon 24 of another patient. Both of these substitutions would change an amino acid residue in the first transmembrane domain of the protein. While neither patient had a milder form of disease, both have survived, and this may be partly owing to the nature of their mutations. Furthermore, “biallelic effects,” as described in xeroderma pigmentosum,28 may also occur in HI, where the interplay between 2 heterozygous mutations determines the severity of the disease. In the 3 cases in this series for which no mutation was found, it is likely that there is a complex deletion or a mutation within an intron, promoter, or other regulatory component of the gene that is not amenable to detection with conventional techniques. Mutation analysis is particularly important if preimplantation or early prenatal diagnosis is being considered in the first trimester. Knowledge of the familial mutation allows earlier diagnosis by amniocentesis or chorionic villous biopsy or in vitro fertilization followed by preimplantation diagnosis.

Management of HI requires a multidisciplinary approach from the outset. The disease is not always fatal and is associated with extracutaneous manifestations. Although there is some delay in achieving developmental milestones, many children are able to attend a mainstream school with appropriate support and adults can enter higher education and live independently. Awareness of this information will provide greater understanding of the disease for those who care for patients with HI.

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