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Evaluation of Patients with Ichthyosis Followed in a Neonatal Intensive Care Unit: A Single Center Experience

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ABSTRACT

Objective: Ichthyosis is a keratinization disorder that is characterized by a defective skin barrier and inability to retain water in the skin. Ichthyosis is extremely rare and mostly hereditary, and its manifestations typically involve dryness, scaling, and hyperkeratosis. Moreover, different clinical findings may be observed depending on the concomitant anomalies. Patients with ichthyosis should be protected from infection and hypernatremic dehydration during the neonatal period. After diagnosis, patients with ichthyosis should be screened for concomitant genetic disorders and their families should be referred to genetic counseling.

Materials and Methods: In this study, ichthyosis cases observed in our neonatal intensive care unit were retrospectively evaluated. We analyzed the genetic analyses and demographic and clinical data of patients hospitalized in our unit over the past 9 years.

Results: Three of the 24 patients evaluated expired during the neonatal period. Genetic analysis was performed on 10 patients, with 8 exhibiting a pathogenic variant. Four of these cases were diagnosed with syndromic ichthyosis, whereas four were nonsyndromic.

Conclusion: Patients with ichthyosis need to be diagnosed early and subsequently screened for accompanying anomalies. In managing this disorder, genetic analysis and counseling are as important as proper skin care, hydration, and infection prevention and should not be overlooked.

Keywords: Ichthyosis, neonatal, syndromic type ichthyosis, nonsyndromic type ichthyosis, genetic.

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INTRODUCTION

Ichthyosis is an often hereditary, heterogeneous keratinization disorder that is characterized by widespread dryness, flaking, scaling, and hyperkeratosis.[1,2] Hereditary ichthyosis involves abnormal epidermal differentiation and can be divided into two subgroups, namely, syndromic and nonsyndromic ichthyosis. Syndromic ichthyosis consists of organ involvement besides skin findings, nonsyndromic types have symptoms only isolated to the skin. Patients with syndromic ichthyosis may exhibit various clinical findings with respect to the accompanying anomaly.[3] Although ichthyosis cases are rare, early diagnosis is vital for proper skin care and identification of these accompanying anomalies.

Owing to the hereditary nature of this disorder, genetic screening and genetic counseling should be considered.[4] In this study, we retrospectively evaluated patients diagnosed and monitored for ichthyosis during the neonatal period. We aimed to contribute to the literature by examining the demographic characteristics, clinical course, and genetic analyses of these cases.

MATERIALS AND METHODS

This study was conducted with the approval of the ethics committee and in accordance with the Helsinki Declaration. The study was carried out at İnönü University Turgut Özal Medical Center. The medical records of cases admitted to the neonatal intensive care unit from January 2012 to December 2021 were retrospectively examined. Patients diagnosed with ichthyosis were included in the study. The cases were evaluated with respect to demographic characteristics (birth weight, gestational week, gender, and concomitant anomalies), family history, and clinical course during admission. Information about the genetic analysis was obtained via an electronic hospital database system. Of the 8 patients who received a genetic diagnosis, 4 were diagnosed with next-generation sequencing analysis, and 3, with Sanger sequencing analysis. For one patient, fluorescent in situ hybridization analysis was studied to reveal the deletion, followed by array CGH analysis to determine the size of the deleted region.

Statistical Analysis

SPSS for Windows version 21.0 packaged software was used for statistical analysis. Frequency and percentages were used to summarize categorical variables. Shapiro–Wilk test was used to determine whether continuous variables exhibited a normal distribution. Normal continuous data were stated as mean±standard deviation, whereas nonnormal continuous data were stated as median (minimum–maximum).

RESULTS

The number of ichthyosis cases admitted to the neonatal intensive care unit in the past 9 years was 24 out of 12,819 patients (0.18%). The gender distribution was 14 females and 10 males. The median gestational age was 37 (28–39) years, with 7 patients being premature. Furthermore, the median birth weight was 2585 (1000–3500) g. Fourteen patients were born to consanguineous parents (first degree), and 8 revealed a family history of ichthyosis. Concomitant minor anomalies were present in 11 patients (45.8%) (Table 1).

All patients were followed closely in the status of dehydration and sepsis during their hospitalization. The median day of hospitalization was 12.5 (3–90) days; 21 patients were discharged with recovery, whereas 2 died due to sepsis and one due to sudden cardiac arrest, totaling three mortalities. During intensive care, 2 patients developed candida-related sepsis, and the other one developed renal failure (Table 1).

Table 1. Patients' demographic characteristics and findings

Gender (M/F n/n)	10/14
Birth weight, (gram)*	2.585 (1000–3500)
Birth week, (week)*	37 (28–39)
Consanguineous marriage, n (%)	14 (58.3)
Family history, n (%)	7 (29.2)
Prematurity, n (%)	7 (29.2)
Additional anomaly, n (%)	Ear anomaly, 2 (8.3)
	Hypothyroidism, 2 (8.3)
	Cleft lip, 1 (4.2)
	Syndactyly in the feet, 1 (4.2)
	Ectropion, 4 (16.6)
	Epilepsy, 1 (4.2)
Day of hospitalization, (day)*	12,5 (3–90)
Mortality rate, n/n (%)	3/24 (12.5)

M: Male; F: Female; *: Values are given as median (min–max).

Genetic analysis was conducted in 10 patients, with 8 exhibiting a pathological variant. Four of these cases included syndromic type ichthyosis, whereas the other four included the nonsyndromic type, based on the classification of ichthyosis consensus conference in 2009 (Table 2).[2]

DISCUSSION

Ichthyosis is a disorder that occurs due to epidermal changes, typically resulting from a defective skin barrier and reduced water-retaining capacity. This increases the risk of hypernatremic dehydration and infection.[5] Prenatal development of ichthyosis can potentially lead to preterm delivery. Neonates with ichthyosis require monitoring and treatment in the intensive care unit provided by tertiary care facilities.[6] Our study comprised seven premature cases; all patients were monitored in the intensive care unit of our tertiary healthcare facility.

The clinical presentation of ichthyosis may vary depending on the type, concomitant anomalies, and personal/environmental factors. Although skin findings may be more evident during the winter, they may vary from mild dryness and scaling in the extremities to scaling and severe widespread thickening. Severe cases may exhibit erythema, palmoplantar keratoderma, ectropion, and heat intolerance, as well as alopecia and reduced sweating.[7–9] Özdemir et al.[10] determined that the prevalence of hypothyroidism was higher in collodion infants in their studies. We discovered that 2 of our patients had hypothyroidism. During the neonatal period, infants with ichthyosis, particularly those with Harlequin and collodion, have an increased risk of mortality due to skin infection, aspiration pneumonia,

Table 2. Patients' genetic analysis results

	Causative gene	Inheritance	DNA variant	Protein change	Mutation type	Databases (in silico analyses) for mutation classification	Type
Case 1	*ABHD5*	AR	c.594dupC (rs387906335) (NM_001355186.2)	p.R199fs*11	Frameshift	MutationTaster: Disease causing ClinVar: Pathogenic	Chanarin–Dorfman syndrome (syndromic type)
Case 2	*ABHD5*	AR	c.594dupC (rs387906335) (NM_001355186.2)	p.R199fs*11	Frameshift	MutationTaster: Disease causing ClinVar: Pathogenic	Chanarin–Dorfman Syndrome (syndromic type)
Case 3	*ABHD5*	AR	c.594dupC (rs387906335) (NM_001355186.2)	p.R199fs*11	Frameshift	MutationTaster: Disease causing ClinVar: Pathogenic	Chanarin–Dorfman Syndrome (syndromic type)
Case 4	*ABHD5*	AR	c.594dupC (rs387906335) (NM_001355186.2)	p.R199fs*11	Frameshift	MutationTaster: Disease causing ClinVar: Pathogenic	Chanarin–Dorfman Syndrome (syndromic type)
Case 5	*TGM1*	AR	c.968G>A (rs121918717) (NM_000359.3)	p.R323Q	Missense	MutationTaster: Disease causing ClinVar: Pathogenic	ARCI1 (nonsyndromic type)
Case 6	*TGM1*	AR	c.968G>A (rs121918717) (NM_000359.3)	p.R323Q	Missense	MutationTaster: Disease causing ClinVar: Pathogenic	ARCI1 (nonsyndromic type)
Case 7	*CYP4F22*	AR	c.844C>T (rs767352854) (NM_173483.4)	p.R282W	Missense	MutationTaster: Disease causing ClinVar: Uncertain significance	ARCI5 (nonsyndromic type)
Case 8	*STS*	XLR	Deletion (arr[GRCh37] Xp22.31(6488721_8097511)x0)		Hemizygous deletion	ClinVar: Pathogenic	XLI (nonsyndromic type)

AR: Autosomal recessive; XLR: X*linked recessive; ARCI: Autosomal recessive congenital ichthyosis; XLI: X-linked ichthyosis.

hypothermia, and hypernatremic dehydration due to transepidermal water loss. The initial treatment approach consists of preventing dehydration due to transepidermal water loss; these infants should be adequately hydrated and cared for in a humidified heated incubator.[11] Topical agents such as emulsifying ointments and retinoids can be applied in skin care.[12] In the case series published in our country, it was emphasized that retinoic acid is beneficial in the treatment of collodion babies.[13] Additionally, during care, rigorous adherence to hygiene norms is required, and the patient's pain must be managed.[14,15] Preventive and supportive care for infants with ichthyosis is known to substantially enhance their quality of life.[16,17] Recent case reports suggest that biological molecules are efficacious against ichthyosis, but this has not been conclusively demonstrated.[18] We closely monitored our patients' hydration levels, and we used sterile mittens and linens to safeguard patients against sepsis. Despite the stringent hygiene standards and fluid support administered to our patients, four infants developed sepsis and one developed renal failure.

In the 2009 ichthyosis consensus by Oji et al.,[3] ichthyosis was classified as syndromic and nonsyndromic. Nonsyndromic ichthyosis involves a late onset compared to syndromic ichthyosis. Clinical management of syndromic ichthyosis presents challenges due to the accompanying anomalies. The clinical findings of syndromic ichthyosis may involve other organs besides the skin; depending on the molecular genetic defects present, conditions such as Netherton syn-

drome, Sjögren–Larsson syndrome, Conradi–Hünermann–Happle syndrome (X-linked Dominant Chondrodysplasia Punctata), Chanarin–Dorfman syndrome, ichthyosis follicularis, atrichia, and photophobia syndrome, and Refsum syndrome could be observed.[8]

Nonsyndromic ichthyoses are disorders that solely involve the skin. These ichthyoses include ichthyosis vulgaris, which is caused by a pathogenic variant in the *FLG* gene; autosomal recessive congenital ichthyosis; X-linked recessive ichthyosis due to genomic deletions, including *STS* on Xp22.3 in up to 90% cases; and keratinopathic ichthyosis, which occurs due to mutations in keratin genes.[8,19] Autosomal recessive congenital ichthyosis is divided into major and minor subtypes; the three major subtypes are Harlequin ichthyosis, classic lamellar ichthyosis, and (nonbullous) congenital ichthyosiform erythroderma, whereas the minor subtypes include self-healing collodion baby and bathing suit ichthyosis.[7] Harlequin ichthyosis represents the most severe form of nonsyndromic ichthyoses associated with perinatal morbidity and potential lethality early in life.[20] *ABCA12* gene analysis is the initial approach in patients with Harlequin ichthyosis. Patients without Harlequin presentation at birth should initially undergo *TGM1* gene analysis. In premature infants with ichthyosis, the *SLC27A4* gene should be examined. The uncommon genetic etiologies of autosomal recessive congenital ichthyosis consist of mutations in *ALOX12B*, *ALOXE3*, *CASP14*, *CERS3*, *CYP4F22*, *LIPN*, *NIPAL4*, *PNPLA1*, and *SDR9C7*.[21] Therefore, establishing the underlying genetic mechanism is crucial for effective genetic counseling. In our study, genetic analysis was conducted on 10 patients, with 2 exhibiting no pathology. Four patients were diagnosed with Chanarin–Dorfman syndrome due to a mutation of the *ABHD5* gene. The other 4 patients were diagnosed with nonsyndromic ichthyosis as a result of two *TGM1*, that is, one *CYP4F22* and one *STS* mutation.

Chanarin–Dorfman syndrome is an autosomal recessive disorder characterized by a reduction of lipolysis activity in various tissues. Homozygous or compound heterozygous pathogenic mutations of the *ABHD5* gene result in ichthyosis and the accumulation of intracytoplasmic lipid droplets. Liver involvement is a significant factor in mortality and morbidity.[22] In our study, 4 patients were diagnosed with a homozygous *ABHD5* mutation. Our patients were siblings from two different families that both involved consanguineous marriages; one family included a parent with a homozygous mutation, whereas the other family included a parent with a heterozygous mutation. The same pathogenic variant was determined in both the two families who were from nearby settlements. Hence, we hypothesized that there may be an increased risk of carrying this variant in that region.

TGM1 and *CYP4F22* gene mutations lead to autosomal recessive congenital ichthyosis (ARCI). Bathing suit ichthyosis, which is caused by biallelic pathogenic variants of the *TGM1* gene, is characterized by the presence of brown and dark gray scales on the trunk (swimsuit area), leaving the extremities and the facial region unaffected.[23] Individuals with *CYP4F22* gene mutations typically exhibit intense erythrodermic skin at birth and milder lamellar ichthyosis or congenital ichthyosis erythroderma phenotypes in further stages of life.[24] In our study, 2 patients were diagnosed with the same homozygous *TGM1* pathogenic variant and were siblings with a family history of consanguineous marriage. Our patient who exhibited a homozygous mutation in the *CYP4F22* gene also had consanguineous parents who were both carriers of this variant.

In terms of diagnosis, family members with similar histories and phenotypes are relatively important. The presence of ichthyosis in male family members in particular helps distinguish ichthyosis that occurs due to steroid sulfatase deficiency that is inherited X-linked recessively. The ichthyosis subtype occurs either due to deletion of Xp22.31 or a point mutation of the STS gene and is observed as a white fish scale pattern during infancy that darkens as it progresses and is particularly apparent in flexor regions of the skin. Affected male patients show increased levels of plasma cholesterol sulfate. In more than 90% of these affected patients, X-linked ichthyosis is the result of a deletion in the Xp22.3 region, including the *STS* gene. An increased deletion size typically results in concomitant conditions such as intellectual deficiency, autism spectrum disorder, and Kallmann syndrome.[19,21] In our study, a hemizygous deletion in the Xp22 region including the *STS* gene was identified in one case. The family had no history of consanguineous marriage, but ichthyosis was present in the mother's male relative members.

CONCLUSION

These uncommon clinical cases should be diagnosed in the early stages and evaluated for concomitant disorders. Fundamental care such as adequate hydration and infection prevention, particularly during the neonatal period, has been linked to a better prognosis. Moreover, conducting genetic analysis is crucial for improved patient management and genetic counseling, as these patients typically exhibit a hereditary background.

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