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MODERN APPROACH TO THE DIAGNOSIS AND TREATMENT OF OCULAR MANIFESTATIONS OF ICHTHYOSIS IN CHILDREN

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Abstract. **Relevance.** Ichthyosis represents a heterogeneous group of inherited disorders of keratinization. One of the main pathogenic mechanisms is associated with mutations in the **FLG** gene, which disrupt the expression of filaggrin—a protein of keratohyalin granules [7]. Insufficient filaggrin decreases the availability of free amino acids in the stratum corneum, impairing water retention. Consequently, patients with ichthyosis vulgaris develop marked xerosis, which is believed to play a role in ocular surface complications. **Objective.** To study the characteristics of ocular manifestations of ichthyosis and to optimize methods for their diagnosis and treatment. **Methods.** Eighty-two children with clinically confirmed congenital ichthyosis were examined. Molecular genetic analysis of the *FLG* gene was performed, focusing on mutations 2282delCAGT, R501X, S3247X, and R2447X. Ophthalmological assessment included visual acuity testing, Schirmer's test, and ocular surface evaluation using the Ocular Surface Disease Index (OSDI). **Results.** The most frequent mutations were 2282delCAGT and R501X, both strongly associated with severe dry eye syndrome and the development of ectropion. In vulgar ichthyosis, the most common ocular manifestations were conjunctivitis (34%) and blepharitis (21%), along with dry eye syndrome (26%). In X-linked ichthyosis, corneal dystrophy was observed in 50% of cases, while congenital bullous ichthyosiform erythroderma was associated with symblepharon (38%) and keratitis (31%). **Conclusion.** Mutations in the *FLG* gene play a significant role in the development of ophthalmological complications in children with ichthyosis. Integration of genetic testing into ophthalmological screening, along with personalized therapeutic strategies, may improve long-term outcomes and quality of life in affected patients.

Keywords: ectropion, ichthyosis, children, dry eye syndrome, scleral lenses, mutations, *FLG*

Ichthyosis is the most common inherited disorder causing pathological skin desquamation, with a prevalence ranging from 1:250 to 1:5000 individuals [1,2]. In patients with ichthyosis, corneal hypoesthesia or complete loss of corneal sensitivity is observed in 25.6–37.1% of cases, frequently leading to the development of keratitis [3,4,5]. Corneal ulcers, lagophthalmos, and lacrimal system pathologies are also characteristic features, and in 47.6–76.7% of cases they result in significant visual impairment, up to complete blindness [6]. The pathogenesis of ichthyosis is primarily associated with a genetically determined defect—impaired expression of filaggrin, a keratohyalin granule protein [7]. Filaggrin deficiency reduces the concentration of free amino acids in the stratum corneum, which are responsible for water retention. This leads to pronounced xerosis in ichthyosis vulgaris and is presumed to contribute to the development of ocular manifestations of the disease [8].

Materials and Methods

We conducted a prospective clinical and genetic study aimed at investigating ophthalmic complications in children with various forms of congenital ichthyosis and their association with mutations in the **FLG** gene. The study included 82 children (66% boys and 37% girls) aged 1 to 18 years, who were followed up at the Pediatric Clinic of TGIU and at the Department of Genodermatoses of the Republican Center of Dermatology and Venereology.

Inclusion criteria:

- Clinically confirmed diagnosis of congenital ichthyosis;
- Availability of informed consent from parents/legal guardians;
- Absence of severe somatic pathology that could affect ophthalmological examination results.

Exclusion criteria:

- Prematurity;
- Congenital ocular anomalies;

• Previous ophthalmic surgery.

Molecular genetic analysis was performed using PCR followed by sequencing. Four key **FLG** gene mutations were assessed:

• 2282delCAGT,

• R501X,

• S3247X,

• R2447X.

These variants were selected because of their known association with severe forms of ichthyosis and impairment of the epidermal barrier.

Ophthalmological examination

The comprehensive diagnostic protocol included:

1. **Visometry** – assessment of visual acuity with and without correction.
2. **Schirmer's test I** – evaluation of tear production, with <10 mm considered pathological.
3. **OSDI questionnaire (adapted for children)** – subjective assessment of dry eye symptom severity.

Results

In 37 examined children with congenital ichthyosis, analysis of **FLG** gene mutations was performed. At least one pathogenic mutation was detected in 68% of cases. The most frequent variants were **2282delCAGT** (36%) and **R501X** (20%), while **S3247X** and **R2447X** were less common (8% and 3%, respectively).

In patients with ichthyosis vulgaris, conjunctivitis and blepharitis were the most common findings (34% and 21% of cases), along with dry eye syndrome in 26%. In X-linked ichthyosis, corneal dystrophy was observed in 50% of cases, whereas congenital bullous ichthyosiform erythroderma was associated with symblepharon and keratitis (38% and 31% of cases, respectively).

Assessment of ocular surface disease severity in children with ichthyosis showed that moderate dry eye syndrome was most common, found in 42% of cases (OSDI score: 20.9 ± 3.8). Schirmer's test averaged 6.1 ± 1.5 mm. A significant strong negative

correlation was identified between dry eye symptom severity and Schirmer's test values, both reflex and basal tear secretion.

We applied a combined treatment strategy for ocular manifestations of ichthyosis, including specific therapy (antioxidants, artificial tears, keratoprotectors, and scleral lenses). Moisturizing and keratoprotective agents reduced subjective complaints in most patients, though the effect was short-lived. Scleral lenses significantly improved ocular surface condition, with clinical recovery observed in 56% of cases. The effectiveness of this method was confirmed by ocular surface disease severity scores, which decreased 3.8-fold compared with baseline (from 20.9 ± 3.8 points to 6.8 ± 3.8 points after treatment, $p<0.05$).

Discussion

This study demonstrated that ophthalmic complications are common in children with congenital ichthyosis and are closely associated with **FLG** mutations. In our cohort, the most significant variants were **2282delCAGT** and **R501X**, which correlated with severe dry eye syndrome and ectropion. These findings are consistent with previous reports highlighting the crucial role of filaggrin deficiency in epithelial barrier dysfunction and the development of ocular surface complications [3,7].

The literature describes **FLG** mutations as risk factors for atopic dermatitis, allergic diseases, and xerosis; however, their role in ichthyosis-related ophthalmopathy has not been sufficiently studied. Our data confirm that carriage of pathogenic **FLG** variants predisposes children to ocular complications, supporting the consideration of genetic screening as an important step in the diagnostic algorithm for this patient group.

Conventional moisturizing therapy proved insufficient for symptom control, consistent with observations from other studies [9,10,11,12]. In contrast, the use of scleral lenses demonstrated a pronounced therapeutic effect, with improvement in subjective symptoms, reduction in keratitis frequency, and prevention of corneal erosions. These results align with published evidence regarding the high efficacy of scleral lenses in severe forms of dry eye disease [13].

Thus, our findings emphasize the need to integrate genetic testing and ophthalmological assessment in the early diagnosis of ichthyosis complications. Such an approach not only enables identification of at-risk patients but also facilitates timely personalized management, including scleral lens fitting and surgical planning.

Conclusions

1. Ophthalmic complications are common in children with congenital ichthyosis (ectropion, dry eye syndrome, conjunctivitis, keratitis) and have a significant impact on disease prognosis and quality of life.
2. Molecular genetic analysis demonstrated that **FLG** mutations (particularly 2282delCAGT and R501X) are associated with more severe ocular manifestations, including pronounced ectropion and tear film deficiency.
3. The use of comprehensive ophthalmological diagnostics (OSDI, Schirmer's test) facilitates early detection of pathological changes of the ocular surface.

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