Background: The neuro-ichthyotic diseases are clinically and genetically heterogeneous. The purpose of this study was to evaluate the clinical and neuroradiological findings and to analyze mutation in 15 patients with neuro-ichthyotic diseases. Materials and Methods: We retrospectively analyzed the records of 15 patients with the diagnosis of neuro-ichthyotic diseases. Results: Eight female and seven male patients (age range 11 months–52 years) were investigated. There were eight patients with Sjögren-Larsson syndrome (SLS), five patients with multiple sulfatase deficiency (MSD), one patient with Chanarin-Dorfman’s syndrome, and one patient with mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia (MEDNIK) syndrome. Parental consanguinity was found in all the patients except one. All patients had ichthyosis. Diagnosis was performed with genetic study. Conclusions: Because biochemical and clinical findings are variable, the diagnosis is difficult in most of the cases. Detailed skin and physical examinations are mandatory in these patients. Genetic tests are necessary for accurate diagnosis.

Keywords: Genetic study, neuro-ichthyotic diseases, skin and physical examination

INTRODUCTION

Ichthyosis, also called disorders of keratinization or cornification, is a heterogeneous group of disorder characterized by a generalized scaling of the skin of varying severity. The great majority of ichthyoses are inherited, but acquired forms can develop. The 2009 consensus classification, based on the clinical phenotype, mode of inheritance, and molecular defect, recognizes two main groups of ichthyosis: nonsyndromic forms and syndromic forms.[1] Among these disorders, the distinctive coexistence of neurological symptoms and ichthyosis is seen in a subgroup of genetic diseases referred to as the neuro-ichthyosis.

The neuro-ichthyotic diseases are clinically and genetically heterogeneous. They include 16 distinct disorders with a known genetic etiology.[2] Many of them affect lipid metabolism, glycoprotein synthesis, or intracellular vesicle trafficking. The existence of biochemical or genetic markers has permitted their reliable diagnosis and provided insight into their clinical variation and pathogenic mechanisms.

There have been many reports on the diseases associated with neuro-ichthyotic diseases.[3-8] Here we present clinical findings and the mutation analysis of 15 Turkish patients with neuro-ichthyotic diseases.

MATERIALS AND METHODS

We evaluated 15 patients diagnosed with neuro-ichthyotic diseases with clinical findings, radiological and mutation analysis. The data were retrospectively collected from the clinic files and included age, sex, consanguinity, family history, clinical symptoms, cerebral magnetic resonance imaging (MRI) findings, nerve conduction studies, and mutation analysis.

The medical histories of all patients were taken, and additionally, physical, neurological, and fundus...
examinations were performed. Cerebral MRI and mutation analysis were performed in all of the patients.

RESULTS
There were 15 patients aged between 11 months and 52 years; 8 were female and 7 were male. Eight of them had Sjögren–Larsson syndrome (SLS), five had multiple sulfatase deficiency (MSD), one had Chanarin–Dorfman’s syndrome (CDS), and one had mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia (MEDNIK) syndrome. Parental consanguinity was found in all the patients except one. Some of the patients were siblings with SLS (patient 1–2, patient 3–4, patient 5–6, and patient 7–8). Ocular examination revealed bilateral glistening dots on the macular region of the retina in 50% patients with SLS. All patients had ichthyosis [Figure 1]. We found cardiac anomaly (secundum atrial septal defect) in two patients with MSD.

The characteristics of all the patients are shown in [Table 1].

DISCUSSION
The combination of neurological disease and ichthyosis defines a heterogeneous group of rare inherited disorders. Despite affected patients share the cutaneous feature of ichthyosis, there is variability in neurological disease. The primary neurological findings are impaired cognition, spasticity, deafness, visual impairment, seizures, and scoliosis.[2]

Sjögren–Larsson syndrome is a neurocutaneous disorder characterized by clinical triad of congenital ichthyosis, diplegia or tetraplegia, and learning disability/mental retardation. It is a rare disease with a prevalence of <0.4 per 100,000.[6] A disturbance of lipid metabolism due to deficiency of the microsomal fatty aldehyde dehydrogenase (FALDH) underlies SLS. Because of the deficiency of this enzyme, there is an accumulation of aldehyde-modified lipids or fatty alcohol in the skin and in the myelin.[2,3]

Ichthyosis is usually the first symptom of SLS. Later in childhood, the complete clinical picture gradually develops, consisting of spasticity in the extremities and learning disability/mental retardation. Seizures are present in one-third of patients. Gånemo et al.[7], in a study of 34 patients with SLS, reported ichthyosis and learning disability in 100%, epilepsy in 38%, complete dependence on a wheelchair for mobility in 59%, and scoliosis in 2.9%. We found ichthyosis and learning disability/mental retardation in 100%, complete dependence on a wheelchair for mobility in 62.5%, epilepsy in 25%, and scoliosis in 12.5%. Brain MRI may be normal in the first few years of life, but older children and adults typically show white matter disease involving the centrum semiovale, corpus callosum, periventricular regions, and parietal and frontal lobes.[9] Typically, white matter lesions in cerebral MRI were found in all our patients.

SLS is caused by mutation in the gene ALDH3A2 for the microsomal FALDH on chromosome 17p11.2. More than 70 mutations in ALDH3A2 are known in SLS patients.[3] Among all the patients with SLS, we identified c.1108-1G>C mutation in the ALDH3A2 gene in four patients, c.24-25CC>TT (p.R9X) mutation in the ALDH3A2 gene in two patients, and c.835T>A (p.Y279N) mutation in ALDH3A2 in two patients.

MSD is a rare, autosomal recessive (OR) in-born error of metabolism characterized by deficient activity of sulfatase enzymes due to mutations in the SUMF1 gene encoding formylglycine-generating enzyme.[9] This enzyme is responsible for the posttranslational activation of sulfatase enzymes via conversion of a crucial cysteine residue to a formylglycine residue.[2,10] Without posttranslational activation, sulfatase enzymes are nonfunctional and various sulfated molecules accumulate in tissues.

The clinical findings of MSD combine symptoms of different sulfatase deficiencies. Patients show neurological deterioration and a neurodegenerative course of disease similar to metachromatic leukodystrophy. In addition, developmental delay, dysmorphism, and organomegaly are present as found
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Table 1: The characteristics of all the patients

| Disorders | Age/sex | Consanguinity | Clinical features | Brain MRI abnormalities | Mutation |
|-----------|---------|---------------|-------------------|-------------------------|----------|
| Patient 1 (SLS) | 12 years/M | + | Ichthyosis, mental retardation, epilepsy, spastic tetraplegia, not walking | Bilateral symmetrical hyperintense lesions in PWM | c.835T>A (p.Y279N) in the ALDH3A2 gene |
| Patient 2 (SLS) | 20 years/M | + | Ichthyosis, mental retardation, spastic tetraplegia, glistening dots, walking | Bilateral symmetrical hyperintense lesions in PWM | c.835T>A (p.Y279N) in the ALDH3A2 gene |
| Patient 3 (SLS) | 8 years/M | + | Ichthyosis, mental retardation, spastic diplegia, walking | Bilateral symmetrical hyperintense lesions in PWM | c.1108-1G>C in the ALDH3A2 gene |
| Patient 4 (SLS) | 13 years/M | + | Ichthyosis, mental retardation, spastic tetraplegia, not walking | Bilateral symmetrical hyperintense lesions in PWM | c.1108-1G>C in the ALDH3A2 gene |
| Patient 5 (SLS) | 19 years/M | + | Ichthyosis, mental retardation, spastic tetraplegia, not walking | Bilateral symmetrical hyperintense lesions in PWM | c.24-25CC>TT (p.R9X) in the ALDH3A2 gene |
| Patient 6 (SLS) | 24 years/F | + | Ichthyosis, mental retardation, spastic tetraplegia, glistening dots, walking | Bilateral symmetrical hyperintense lesions in PWM | c.24-25CC>TT (p.R9X) in the ALDH3A2 gene |
| Patient 7 (SLS) | 43 years/M | + | Ichthyosis, mental retardation, epilepsy, spastic tetraplegia, glistening dots, not walking | Bilateral symmetrical hyperintense lesions in PWM | c.1108-1G>C in the ALDH3A2 gene |
| Patient 8 (SLS) | 52 years/F | + | Ichthyosis, mental retardation, epilepsy, spastic tetraplegia, scoliosis, glistening dots, not walking | Bilateral symmetrical hyperintense lesions in PWM | c.1108-1G>C in the ALDH3A2 gene |
| Patient 9 (MSD) | 18 months/F | − | Ichthyosis, dysmorphic features, developmental delay, epilepsy, scoliosis, dysostosis multiplex, hepatosplenomegaly | Hyperintense lesions in PWM | c.739G>C (p.G247R) in the SUMF1 gene |
| Patient 10 (MSD) | 11 months/M | + | Ichthyosis, developmental delay, hepatosplenomegaly | Hyperintense lesions in PWM | c.739G>C (p.G247R) in the SUMF1 gene |
| Patient 11 (MSD) | 18 months/F | + | Ichthyosis, developmental delay, deafness, secundum atrial septal defect, dysostosis multiplex | Hyperintense lesions in PWM | c.739G>C (p.G247R) in the SUMF1 gene |
| Patient 12 (MSD) | 16 months/F | + | Ichthyosis, developmental delay, secundum atrial septal defect, dysostosis multiplex, hepatosplenomegaly | Hyperintense lesions in PWM | c.739G>C (p.G247R) in the SUMF1 gene |
| Patient 13 (MSD) | 6.5 years/F | + | Ichthyosis, developmental delay, deafness, dysostosis multiplex, epilepsy, hepatosplenomegaly | Hydrocephaly, ventriculoperitoneal shunt | p.S155P (c.463T>C in the SUMF1 gene |
| Patient 14 (MEDNIK syndrome) | 10 years/F | + | Ichthyosis, mental retardation, deafness, enteropathy, keratodermia, not walking | Cerebral atrophy | c.356_357insG (p.D122Gfs*18) in AP1S1 gene |
| Patient 15 (CDS) | 7 years/F | + | Ichthyosis, mental and growth retardation, cataract, nystagmus, deafness, hepatomegaly | Normal | c.343 A>G (p.S115G) in the ABHD5 gene |

PWM = periventricular white matter

in various mucopolysaccharidosis (MPS).\textsuperscript{[11]} Patients with MSD may also have mental retardation, coarse face, seizures, tetraplegia, visceromegaly, ichthyosis, and dysostosis.\textsuperscript{[2,11]} Brain MRI shows hyperintense T-2 signals in posterior periventricular and subcortical white matter.\textsuperscript{[2]} In our patients, we detected general hypotonia, mental retardation, coarse face, ichthyosis, and hepatosplenomegaly. Also, we found cardiac anomaly in two patients. To our knowledge, cardiac anomaly was not reported previously in the literature. Deafness was seen in two patients. Two patients had epilepsy. Dysostosis multiplex was detected in four of our patients. Typically, white matter lesions in cerebral MRI were found in all patients except one [Figure 2].
This patient had hydrocephalus. al-Moutaery et al.\[12\] reported a case of 2.5-year-old boy with Saudi variant of MSD. He had cervical cord compression and hydrocephalus without white matter changes in the brain as in our patient. We detected homozygous missense mutation c.739G>C (p.G247R) in the SUMF1 in four patients and homozygous mutation p.S155P (c.463T>C) in the SUMF1 gene in one patient.

CDS is a rare, inherited, OR disorder of lipid metabolism characterized by ichthyosis, lipid vacuoles in leukocytes, and involvement of several internal organs.\[13\] It is caused by mutation in the CGI-58 gene, which mediates acylation of lysophosphatidic acid.\[14\] The majority of cases come mostly from the Mediterranean and Middle East countries, especially from Turkey and in consanguineous marriages.\[14\] Our case was also born to consanguineous parents, and she had ichthyosis, mental and growth retardation, cataract, nystagmus, deafness, and hepatomegaly. We described homozygous mutation p.S115G (c.343A>G) in the ABHD5 gene.

MEDNIK syndrome is an OR disease characterized by mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma.\[2,15,16\] Neurological deficits include psychomotor retardation, hypotonia, peripheral neuropathy, and sensorineural deafness. Gastrointestinal symptoms such as congenital diarrhea may be present. Patients have elevated levels of very long-chain fatty acids, suggesting peroxisomal dysfunction. The disease was first described in four French-Canadian families who segregated a founder mutation in APISI, which encodes a subunit of adapter protein AP-1 complex that participates in endocytic vesicle assembly, protein cargo sorting, and vesicular trafficking.\[2,15,16\] The diagnosis of MEDNIK syndrome requires DNA analysis of APISI. There is no specific therapy. A 10-year-old girl was presented with ichthyosis and gross developmental delay in our hospital. The patient was admitted to other hospital for evaluation of these symptoms. But she was not diagnosed with laboratory analyses. Our patient had mental retardation, enteropathy, deafness, ichthyosis, and keratoderma. We found a novel homozygous p.D122Gfs*18 (c.356_357insG) mutation in APISI gene in the patient.

The differential diagnosis of these neuro-ichthyotic disorders include SLS; MSD; Refsum disease; CDS; trichothiodystrophy; ELOVL4 deficiency; keratitis, ichthyosis, deafness (KID) syndrome; Gaucher’s disease type 2; and vesicle-trafficking disorders [Cerebral dysgenesis, neuropathy, ichthyosis and keratoderma (CEDNIK) syndrome, MEDNIK syndrome, and Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome].\[2,17\] Most of these disorders are caused by genetic defects in lipid metabolism, glycoprotein synthesis, or intracellular vesicle trafficking.\[13\] Neuroimaging shows diffuse white matter involvement in SLS, hypomyelination in trichothiodystrophy, posterior periventricular and subcortical white matter signal changes in MSD, and variable cerebral dysgenesis in vesicle-trafficking disorders.

In conclusion, detailed skin and physical examination is mandatory in a neurology clinic for this patient. The combination of neurological disease and ichthyosis defines a heterogeneous group of rare inherited disorders that present in infancy through early adulthood. Impaired cognition, spasticity, deafness, visual impairment, and/or seizures are the primary neurological findings. The clinical features of some of the neuro-ichthyoses are distinct enough to allow their clinical recognition, but confirmatory biochemical or genetic tests are necessary for accurate diagnosis.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.
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