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Recognition and Diagnosis of Neuro-Ichthyotic Syndromes

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Abstract

The combination of neurologic disease and ichthyosis defines a heterogeneous group of rare inherited disorders that present in infancy through early adulthood. Although affected patients share the cutaneous feature of ichthyosis, there is variability in the nature and severity of neurologic disease. Impaired cognition, spasticity, sensorineural deafness, visual impairment, and/or seizures are the primary neurologic findings. Most of these disorders are caused by genetic defects in lipid metabolism, glycoprotein synthesis, or intracellular vesicle trafficking. 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. Treatment of the ichthyosis is largely symptomatic, and except for Refsum's disease, there are no effective pathogenesis-based therapies for the neurologic disease.

Keywords

ichthyosis; lipids; mutation; skin; myelin

Neurocutaneous diseases comprise a large and heterogeneous group of disorders that are predominantly genetic in nature. Among these disorders, the distinctive coexistence of neurologic symptoms and ichthyosis is seen in a subgroup of genetic diseases referred to as the neuro-ichthyoses. These diseases may appear superficially similar at a clinical level and can seem bewildering for the clinician who first encounters a patient. Upon closer inspection, however, many neuro-ichthyoses have distinguishing historical and clinical features that allow them to be recognized and reliably diagnosed using biochemical or DNA tests. The number of neuro-ichthyotic syndromes with identified genetic etiologies has increased over the past decade, and knowledge about their molecular etiologies has expanded accordingly. Although effective treatments for most of these disorders remain an elusive challenge, insights into therapeutic approaches are starting to emerge.

The major neuro-ichthyotic syndromes will be reviewed with an emphasis on their clinical recognition and a practical diagnostic approach provided that can be used by the neurologist and other subspecialists.

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Clinical Recognition of Ichthyosis

Neurologists, and many other physicians, may not recognize the presence of ichthyosis in patients, in part due to the rarity of the symptom, the failure to focus on the skin in patients who have severe neurologic disease, the wide variation in its severity—even in the same patient—and the general tendency to simply ascribe it to “dry skin.” In fact, mildly affected patients may partially mask the cutaneous symptoms by the liberal use of moisturizing lotions. It is uncommon, however, to miss ichthyosis in patients who have more severe forms, especially those that present at birth. Some newborn infants are covered by a parchment-like “collodion membrane,” which resolves over the first weeks of life, leaving behind a dry, scaly appearance. To assist in its recognition, variation in the appearance of ichthyosis is illustrated in Fig. 1.

Neuro-Ichthyotic Syndromes of Known Etiology

The neuro-ichthyotic diseases are clinically and genetically heterogeneous. They include 16 distinct disorders with a known genetic etiology (Table 1). 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.

Sjögren-Larsson’s Syndrome

Sjögren-Larsson’s syndrome (SLS) is the most widely recognized form of neuro-ichthyosis. The disease is characterized by the presence of ichthyosis, spastic diplegia or tetraplegia, cognitive delay, seizures, and a maculopathy with glistening white dots.[1] The cutaneous abnormalities are usually present at birth, at which time the skin appears erythematous and hyperkeratotic. About 15% of newborn infants have a collodion membrane. The cutaneous disease in SLS has a characteristic pruritic nature, and the itchiness is an agonizing feature for some patients. Neurologic symptoms are rarely present in the first few months of life, but appear later in the first year with delay in achieving motor milestones due to spastic diplegia or tetraplegia. Intellectual impairment varies from mild to profound, and rare patients are cognitively normal. Most patients have pseudobulbar dysarthria and exhibit speech delay beyond that expected from their cognitive impairment. Ophthalmologic examination shows perifoveal glistening white dots in ~85% of patients, but these retinal abnormalities may only appear after infancy. Myopia and photophobia are common. Seizures occur in 30% of patients. 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.[2] Magnetic resonance spectroscopy (MRS) characteristically reveals unusual lipid peaks at 1.3 ppm and 0.9 ppm in the affected white matter. Peripheral nerve function is unaffected. The neurologic disease is usually static and patients routinely survive into adulthood.

Sjögren-Larsson’s syndrome is caused by mutations in the *ALDH3A2* gene that codes for fatty aldehyde dehydrogenase.[3] Fatty aldehyde dehydrogenase is necessary for the oxidation of long-chain aldehydes and alcohols to fatty acids. Deficiency of this enzyme leads to accumulation of these lipids in skin and brain, which is thought to be directly responsible for

the symptoms.[1] Fatty aldehydes and alcohols intercalate into membranes and may disrupt myelin by physically altering its membrane structure or forming covalent Schiff-base adducts with myelin lipids and proteins. In the skin, stratum corneum membranes are defective, which results in a leaky water barrier and reactive hyperkeratosis.[4]

The diagnosis of SLS requires measurement of fatty aldehyde dehydrogenase in cultured skin fibroblasts or demonstration of mutations in *ALDH3A2*, which are detected in > 95% of patients.

The ichthyosis in SLS is improved with topical moisturizing lotions, keratolytic agents, and systemic retinoids, but therapy of the neurologic disease is limited. Botox injections are a temporary measure for the spasticity in most patients, who ultimately require surgical procedures.

Neutral Lipid Storage Disease With Ichthyosis

Neutral lipid storage disease with ichthyosis (NLSDI) (also known as Chanarin-Dorfman's syndrome) is characterized by congenital ichthyosis, mental retardation, neurosensory deafness, ataxia, hepatomegaly, myopathy, and cardiomyopathy.[5] There is considerable clinical variation and some patients have normal intelligence or lack liver disease. The ichthyosis may have a pruritic nature. Myopathy is associated with elevated serum creatine kinase and abnormal electromyography (EMG) studies. Progressive neurodegeneration is not typical.

Neutral lipid storage disease with ichthyosis is caused by mutations in the *CGI-58* gene (also known as*ABHD5*), which codes for a protein that stimulates triglyceride hydrolysis.[6] A convenient diagnostic finding is the presence of cytoplasmic lipid droplets in tissues. Examination of a peripheral blood smear reveals vacuolated neutrophils and eosinophils (Jordan's anomaly) due to triglyceride storage, although serum triglycerides are normal. The ichthyosis is likely caused by impaired hydrolysis of fatty acids from triglyceride stores, which are normally used for synthesis of ω-hydroxy-acylceramide, a key lipid component of the stratum corneum membranes required for the epidermal water barrier.[7] The mechanism for neurologic disease has not been elucidated. Mutation analysis of the *CGI-58* gene is required to confirm the diagnosis. The skin can be treated with topical moisturizing lotions, but no specific therapy is available for the neurologic symptoms.

Refsum's Disease

Refsum's disease, also termed hereditary sensory motor neuropathy type IV, is an autosomal recessive disorder caused by mutations in the *PHYH* gene that encodes phytanoyl-CoA hydroxylase. This enzyme is necessary for peroxisomal fatty acid α-oxidation of phytanic acid, a methyl branched-chain fatty acid that is derived from the diet.[8] Due to defective α-oxidation, patients with Refsum's disease slowly accumulate phytanic acid in tissues, resulting in clinical symptoms.[9] The age of symptom onset is quite variable, but typically begins insidiously in late childhood with loss of night vision due to retinitis pigmentosa, and anosmia, which is an almost universal finding. Deafness, ataxia, ichthyosis, and polyneuropathy slowly develop over the next 10 to 15 years. Cognition is not affected. Cardiac arrhythmias are frequently seen and can cause premature death. Sudden death can

rarely occur as a result of acute release of phytanic acid from the liver following stress-induced catecholamine release or infection.

The diagnosis of Refsum's disease is made by demonstrating elevated plasma phytanic acid concentrations >200 μmol/L (normal <3). Mutation analysis of two genes will identify >95% of patients with Refsum's disease. More than 90% of patients have genetic mutations in *PHYH,* and the remaining patients have mutations in *PEX7*, which is necessary for import of phytanoyl-CoA hydroxylase into peroxisomes.

Treatment of Refsum's disease is initiated by removal of phytanic acid through plasmapheresis or lipid apheresis. Dietary restriction of phytanic acid through elimination of dairy products and certain vegetables subsequently reduces phytanic acid levels by 50 to 70% and typically resolves the ichthyosis, sensory neuropathy, and ataxia. Retinitis, anosmia, and deafness, however, may not improve with dietary therapy. Long-term dietary therapy is effective in limiting clinical progression of symptoms. Avoidance of rapid weight loss or fasting is recommended as this can precipitate the acute release of phytanic acid from lipid stores. The intestinal lipase inhibitor, Orlistat has shown some efficacy in reducing phytanic acid absorption with less-strict dietary therapy.[10]

Gaucher's Disease Type 2

Some infants with Gaucher's disease type 2 are born with a collodion membrane and exhibit ichthyosis, contractures, and dysmorphic facial features.[11] They develop opisthotonic posturing, seizures, hypertonicity, hepatosplenomegaly, and strabismus. The neurologic disease progresses over the first few months with dysphagia, cachexia, apnea, and a fatal outcome in the first year of life.

Gaucher's disease type 2 is caused by mutations in the *GBA* gene for glucocerebrosidase.[12] Deficient activity of this lysosomal enzyme results in accumulation of glucosylceramide in brain and most other tissues. The neurologic disease may be caused by accumulation of glucosylsphingosine. In the skin, glucocerebrosidase normally hydrolyzes glucosylceramide to produce ceramide, which is a major lipid in the membranes of the stratum corneum. With reduced ceramides, the membranes are structurally abnormal and the epidermal water barrier is impaired, resulting in ichthyosis. The diagnosis is made by testing leukocytes for enzyme activity or detecting mutations in *GBA*. There is no effective therapy for this form of Gaucher's disease.

ELOVL4 Deficiency

Very long-chain fatty acids (VLCFA) >22 carbons long are essential components of certain lipids, such as acylceramide in skin and sphingolipids in brain. Very long-chain fatty acids are synthesized through elongation of shorter fatty acids, which is catalyzed by microsomal elongating enzymes that sequentially add 2-carbons to the growing fatty acid chain. Seven elongating enzymes (designated ELOVL1–7) are known in man. Patients who carry recessive mutations in the gene for ELOVL4 have recently been reported to have congenital ichthyosis, intellectual disability, seizures, and spastic quadriparesis.[13] The ichthyosis appears erythematous and patchy. Brain magnetic resonance imaging (MRI) in one patient showed brain atrophy and delayed myelination. Seizures are recalcitrant to anticonvulsant

therapy and survival appears limited. The pathogenic mechanism for neurologic and cutaneous symptoms presumably arises from deficient VLCFA-containing lipids. An *ELOVL4*$^{-/-}$ knockout mouse dies within hours of birth due to profound deficiency of VLCFA-containing acylceramide in skin that results in a defective epidermal water barrier.[14] The diagnosis of ELOVL4 deficiency in man is made by mutation analysis of the *ELOVL4* gene. Interestingly, certain dominant mutations in *ELOVL4* cause a form of juvenile macular dystrophy (Stargardt's disease type 3) without the neuro-ichthyotic symptoms. No effective therapy is known.

Multiple Sulfatase Deficiency

Multiple sulfatase deficiency (MSD) is a rare, autosomal recessive inborn error of metabolism characterized by deficient activity of sulfatase enzymes due to mutations in the *SUMF1* gene encoding formylglycine-generating enzyme.[15] This enzyme is responsible for the posttranslational activation of sulfatase enzymes via conversion of a crucial cysteine residue to a formylglycine residue.[16] Without posttranslational activation, sulfatase enzymes are nonfunctional and various sulfated molecules accumulate in tissues.

The clinical features appear as an amalgam of single sulfatase enzyme deficiencies. Similar to metachromatic leukodystrophy, multiple sulfatase deficiency patients exhibit neurodegenerative disease in early childhood due to central nervous system (CNS) and peripheral demyelination and loss of sensory and motor functions. They also develop mental retardation, hepatosplenomegaly, coarse facies, and corneal clouding as seen in patients with mucopolysaccharidoses. Ichthyosis and skeletal changes reffect enzyme deficiencies of steroid sulfatase (X-linked ichthyosis) and arylsulfatase E (chondrodysplasia punctata), respectively. The unique combination of neurodegeneration, coarse facial features, hepatosplenomegaly, and ichthyosis is not seen in other neuro-ichthyotic disorders. However, the sequential appearance of these clinical signs often delays the diagnosis of MSD.

Brain MRI shows hyperintense T-2 signals in posterior periventricular and subcortical white matter. X-ray findings of chondrodysplasia punctata may be seen. Urine glycosaminoglycans and sulfatides are often elevated. The molecular diagnosis is confirmed by measuring sulfatase enzyme activities in leukocytes and sequencing the *SUMF1* gene. There appears to be a correlation between *SUMF1* genotype and clinical severity.[17]

Steroid Sulfatase Contiguous Gene Deletion

Contiguous gene deletions of the short arm of the X chromosome (Xp22.3) involving steroid sulfatase (*STS*) and neighboring genes can present with ichthyosis and neurologic symptoms.[18,19]

Small deletions in *STS* are a frequent cause of isolated steroid sulfatase deficiency (X-linked ichthyosis), a common disorder that affects 1 in 1500 males and presents with ichthyosis in the first weeks of life. This enzyme normally metabolizes cholesterol sulfate, which accumulates in the skin of patients and causes the ichthyosis. Larger contiguous gene deletions of Xp22.3 can involve several notable genes for mental retardation, short stature, chondrodysplasia punctata, and Kallman's syndrome (hypothalamic hypogonadism and

anosmia).[18,19] Depending on the size of the microdeletion of Xp22.3, patients can present with ichthyosis and any combination of gene-related symptoms. Xp22.3 deletions can be detected by microarray comparative genomic hybridization or fluorescent in situ hybridization (FISH) using a *STS* probe.

Glycoprotein Synthesis Disorders: Dolichol Kinase and Steroid 5α-Reductase Type-3 Deficiency

Two inherited disorders of glycoprotein synthesis with prominent neuroichthyotic symptoms have recently been recognized. Both disorders are caused by mutations in genes that are necessary for the synthesis of dolichol-phosphate, which is a phosphorylated very long-chain isoprenoid lipid alcohol that functions as the N-glycan acceptor for glycoprotein biosynthesis.

*DOLK (*or *DK1)* codes for dolichol kinase, an enzyme that catalyzes the final step in synthesis of dolichol-phosphate. Mutations in *DOLK* have been described in four patients, who exhibited ichthyosis, hypotonia, seizures, tetraplegia, microcephaly, nystagmus, and alopecia.[20] Some patients had dilated cardiomyopathy. All died in the first year of life.

Patients with deficiency of steroid 5α-reductase type-3, which catalyzes the penultimate step in dolichol-phosphate synthesis, have clinical features of early visual impairment with various eye malformation (hypoplasia or colobomas of the retina and iris, congenital cataracts, and optic atrophy), nystagmus, cerebellar hypoplasia, ataxia, hypotonia, mental retardation, and ichthyosis or dry skin.[21] Some had heart malformations. Mutations in the *SRD5A3* gene are causative.

The pathogenic mechanisms in both disorders are not clear, but undoubtedly involve deficient synthesis of key glycoproteins in the skin, brain, and other organs. The diagnosis can be supported by detecting abnormally glycosylated serum transferrin, but requires confirmatory mutation analysis of the *DOLK* or *SRD5A3* genes. There is no effective therapy for either disease.

Keratitis-Ichthyosis-Deafness Syndrome

Keratitis, ichthyosis, and deafness (KID) syndrome is a rare sporadic or autosomal dominant congenital disorder that is caused by mutations in the *GJB2* gene encoding the gap junction protein connexin-26.[22,23] Gap junctions are composed of hexameric connexin proteins that form channels to allow exchange of ions, metabolites, and small proteins between the cytoplasm of adjacent cells. Mutated connexin-26 results in functional defects in gap junctions, which allow increased calcium influx and cell necrosis.[24] Connexin-26 mutations are also a common cause of genetic nonsyndromic deafness.

KID patients develop a vascularizing keratitis that leads to decline in visual acuity and possibly blindness.[24] Sensorineural deafness is the primary neurologic manifestation. Cutaneous findings include ichthyosiform erythroderma, palmoplantar keratoderma, erythematous verrucous lesions, and an aged facial appearance. Scarring alopecia and onycho-dystrophy are frequently present. Patients are at increased risk for developing squamous cell carcinomas and inflammatory nodules.[23] The diagnosis is based on

dermatologic, ophthalmologic, and hearing evaluations, and confirmed with molecular analysis of *GJB2*. No specific therapy exists for the disease. A significant number of familial cases have been reported and the possibility of germinal mosaicism should be considered during genetic counseling.[23]

Disorders of Vesicle Trafficking: CEDNIK Syndrome, MEDNIK Syndrome, and ARC Syndrome

CEDNIK Syndrome—CEDNIK syndrome is a rare, autosomal recessive disease named for its defining features of cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma.[25,26] The clinical symptoms of the patients progress with age. During the first 4 months, patients exhibit roving eye movements, poor head and trunk control, microcephaly, and failure to thrive. Facial dysmorphisms are apparent, including elongated faces, antimongolian eye slant, mild hypertelorism, and a flat broad nasal root. Later in the first year of life, ichthyosis and palmoplantar keratoderma appear. Psychomotor retardation becomes apparent between 8 and 15 months. MRI of the brain displays corpus callosum abnormalities and cortical dysplasia with pachygyria and polymicrogyria. Loss of deep tendon reflexes is associated with low amplitude responses on peripheral nerve conduction studies. Muscle biopsies show neurogenic atrophy. Ophthalmologic examination reveals hypoplastic optic disks and macular atrophy. Many patients do not survive beyond childhood.

CEDNIK syndrome is caused by mutations in *SNAP29* that leads to decreased soluble n-ethylmaleimide sensitive factor receptor (SNARE) protein SNAP29 that mediates endocytic vesicle trafficking between organelles and plasma membrane.[27] The decrease in SNAP29 leads to abnormal endocytic vesicle maturation, fusion, and secretion in tissues.[25] Lamellar body vesicles in the skin do not mature and fuse properly with the plasma membrane to release their cargo membrane contents between the stratum granulosum and stratum corneum, which results in diminished stratum corneum membranes and a leaky epidermal water barrier. SNAP29 deficiency also results in defective endocytic recycling of β1-integrin required for cell migration, which may underlie the neuronal migration defect in CEDNIK syndrome.[27] The diagnosis requires DNA analysis of *SNAP29*. No specific therapy exists.

MEDNIK Syndrome—MEDNIK syndrome is an autosomal recessive disease characterized by mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma.[28] The patient's facial features can appear mongoloid with a high forehead. Additional cutaneous symptoms include erythrodermia and erythrokeratodermia variabilis. Neurologic 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 *AP1S1*, which encodes a subunit of adapter protein AP-1 protein complex that participates in endocytic vesicle assembly, protein cargo sorting, and vesicular trafficking. Like CEDNIK syndrome, the mechanisms for ichthyosis and impaired development of various neural networks may be related to abnormal endocytic vesicle trafficking. The

diagnosis of MEDNIK syndrome requires DNA analysis of *AP1S1*. There is no specific therapy.

ARC Syndrome—Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare, autosomal recessive multisystem disorder caused by mutations in the *VPS33B* gene, which codes for a protein that interacts with SNARE proteins and functions in intracellular protein and vesicle trafficking.[29] One-half of ARC patients have associated ichthyosis.[30] The arthrogryposis is thought to be secondary to in utero muscle atrophy from peripheral denervation. Autopsy results have demonstrated alterations in the motor neurons of the anterior horn of the dorsal spinal cord.[31] Neurologic symptoms include hypotonia and global developmental delay. MRI of the brain may reveal agyria and loss of sulci consistent with defective neuronal migration. Renal tubular dysfunction ranges from isolated renal tubular acidosis to a more severe renal Fanconi syndrome with glucosuria, proteinuria, aminoaciduria, phosphaturia, and bicarbonate wasting. A kidney ultrasound typically shows nephrocalcinosis or small dysplastic kidneys. Cholestasis with elevated transaminases and hyperbilirubinemia completes the triad of ARC syndrome. Liver biopsies show a wide spectrum of changes including paucity of bile ducts, lipofusion deposition, bile plugs, bile duct proliferation, giant cell hepatitis, and portal tract fibrosis. Associated dysmorphic features include prominent occiput, posteriorly angulated and low set ears, flattened nasal bridge, upslanting palpebral fissures, simian crease, high arched palate, beaked nose, small anterior fontanel, lax skin, low implantation of the thumb, and cryptorchidism. Frequent complications of the disease include hypernatremic dehydration and polyuria. Most patients with this disorder die before 1 year of age from sepsis, severe dehydration, or acidosis.[31] The diagnosis is confirmed by DNA analysis.

Trichothiodystrophy (TAY SYNDROME)—Trichothiodystrophy (TTD) is a rare, autosomal recessive neuroectodermal disease that features brittle hair and a variety of skin and systemic abnormalities.[32] Patients have mutations in one of four genes (*XPD*, *XPB*, *P8/TTDA*, *TTDN1*) resulting in abnormal production of a multiprotein complex that functions as transcription factor-IIH (TFIIH) and is involved in DNA excision repair.[33] TFIIH functions in both basal and activated transcription of many genes expressed in skin and brain. The nature and severity of symptoms in TTD correlate with the amount of dysfunctional TFIIH and reduced gene transcription.

Affected infants may have low birth weight and a collodion membrane at birth.[32] Neurologic abnormalities include developmental delay, microcephaly, and ataxia. Neuroimaging reveals dysmyelination, cerebellar atrophy, and dilated ventricles. Brittle, sulfur-deficient hair with a “tiger-tail” banding under polarized light microscopy is the defining clinical sign. Additional findings include ichthyosis (65%), short stature, photosensitivity, and increased incidence of infections. Clinical features of TTD, such as age of clinical symptom and mortality, vary greatly. Mortality rate is 20-fold higher than the general population. Infection, especially sepsis, is the most common cause of death.

TDD is usually suspected from the constellation of clinical features, including the characteristic hair abnormality. DNA analysis will show mutations in *XPD*, *XPB*, *P8/TTDA*

or *TTDN1*. Treatment of TTD is supportive and multidisciplinary. Prevention of infection is an important component of effective management.

Disorders with Low Incidence of Ichthyosis and Neurologic Disease

Some disorders are associated with a low (<25%) incidence of ichthyosis and variable neurologic symptoms. These include rhizomelic chondrodysplasia punctata and X-linked chondrodysplasia punctata (Table 1).

Neuro-Ichthyotic Syndromes of Unknown Etiology

Several neuroichthyotic syndromes for which no etiology is known have been reported (see Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/omim). Many of these disorders are less well characterized and some have been reported only in a single pedigree.

Diagnostic Approach to the Neuro-Ichthyoses

The diagnosis of a neuro-ichthyotic disorder is typically delayed until the neurologic and cutaneous symptoms appear together. Most patients present with isolated skin manifestations at birth or later in infancy, but in the absence of other systemic findings, a consulting dermatologist erroneously concludes that the patient has a form of pure ichthyosis. Similarly, in some disorders, neurologic symptoms may precede the onset of the skin disease. The recognition that both organ systems are affected is usually the key to diagnosing these diseases.

The diagnostic approach for patients with neuro-ichthyosis is outlined in Table 2. The physician should begin by collecting as much clinical information as possible using Table 1 as a guide. A clinical geneticist should be consulted to evaluate family history and provide expertise in dysmorphology. Consultations by ophthalmologists and audiologists are mandatory to determine whether ocular abnormalities or deafness exist. Additional clinical and laboratory tests are particularly useful to define the extent of neurologic disease and narrow down the differential diagnosis. Brain MRI and MRS should be done on all patients to reveal congenital dysplasia, white matter disease, or abnormal lipid peaks. For appropriate patients, cardiovascular evaluation with echocardiogram and electrocardiogram is indicated. A skin biopsy for routine histologic analysis with light microscopy is of limited value for diagnosing most of the ichthyoses because these diseases typically exhibit nonspecific findings of hyperkeratosis. However, a search for lipid inclusions in the skin is worthwhile, and electron microscopy may reveal characteristic structural abnormalities in some disorders.[34] Routine laboratory testing should include serum transaminases, creatine kinase, and examination of a blood smear to search for vacuolated leukocytes, which is a diagnostic finding for NLSDI. Several more-specialized biochemical tests, including glycosylated transferrin, lysosomal enzymes, and peroxisomal markers, should help pin down the diagnosis or justify more targeted genetic testing. Ultimately, mutation analysis is necessary for the diagnosis of many of these diseases.

Despite a thorough clinical and laboratory workup, a significant proportion of neuro-ichthyotic patients remain undiagnosed at this time. In the absence of a positive family

history, it is possible that a patient may have two distinct diseases affecting the skin and nervous system, especially if consanguinity exists. With thorough clinical characterization and the application of next-generation DNA sequencing to these patients, however, we can expect new neuro-ichthyotic diseases to be discovered at an increasing pace.

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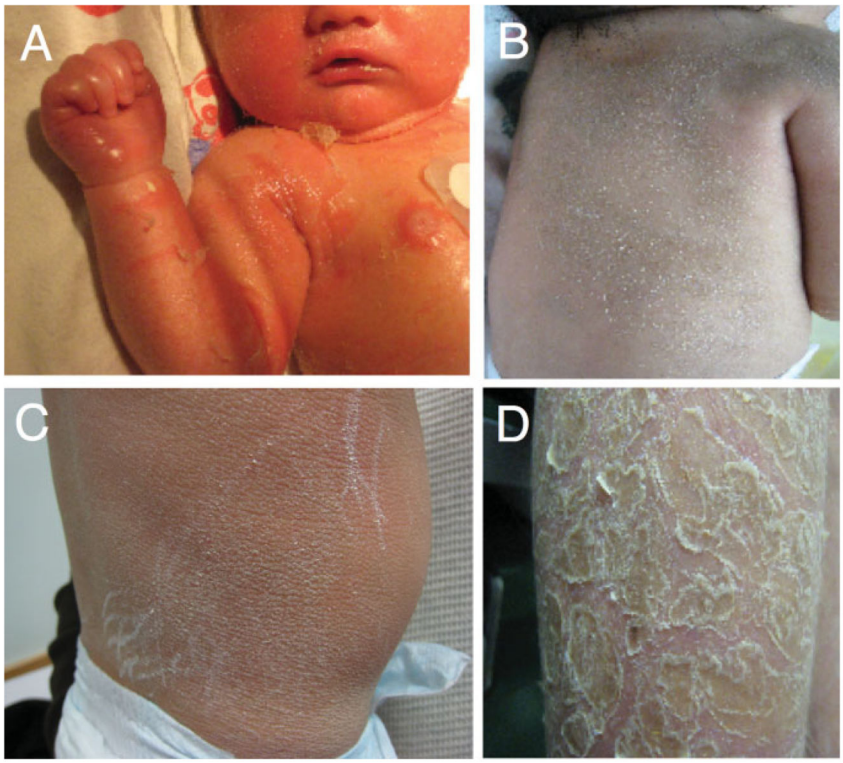

Figure 1.

Variation in the appearance of ichthyosis. (A) Newborn infant with healing collodion membrane. Note the tight, shiny skin on the hand and the areas of desquamation with underlying erythema. The skin later developed hyperkeratosis with scaling. (B) Fine scales on the back and shoulders of a 10-month-old infant with developmental delay. (C) Thick hyperkeratotic skin with a lichenified appearance on the trunk of a 2-year-old infant with Sjögren-Larsson's syndrome. Note excoriations due to pruritus. (D) Large lamellar-like scales on the lower leg of a patient with Sjögren-Larsson's syndrome.

Table 1

Clinical Features of Neuro-Ichthyotic Disorders with a Known Genetic Etiology*

Disorder	Gene Defect	Impaired Cognition	Dysmorphic Facies	Peripheral Neuropathy	Deafness	Eye Abnormality	Seizures	Abnormal Hair	Brain MRI Abnormalities	Associated Clinical Features
Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome	*VPS33B*	±	±	+	−	−	−	−	± Brain dysgenesis	Peripheral denervation of muscles, 50% have ichthyosis, early lethality
CEDNIK syndrome (Cerebral dysgenesis, neuropathy, ichthyosis and palmoplantar keratoderma syndrome)	*SNAP29*	+	+	+	+	± Visual impairment, OptN, macular atrophy	−	± Brittle course hair, ± scarring alopecia	Brain dysgenesis, ± hypoplastic corpus callosum	Failure to thrive, early death
Chondrodysplasia punctata, X-linked recessive	*ARSE*	±	+	−	+	± Cat	−	−	NE	Ichthyosis <20%, punctate epiphyseal calcifications, hypoplastic nasal cartilage and distal phalanges, short stature
Dolichol kinase deficiency	*DOLK*	?	−	−	−	± Nyst	+	Alopecia ±	NE	Hypotonia, spastic tetraplegia, microcephaly. ± DCM, early death.
ELOVL4 deficiency	*ELOVL4*	+	±	−	−	± Pp	+	−	Brain atrophy, deficient myelin	Spastic quadriparesis, inguinal hernias, abnormal VEP
Gaucher's disease type 2	*GBA*	+	±	−	−	−	+	−	NE	Congenital ichthyosis (±), hepatosplenomegaly, neuroregression
Keratitis-ichthyosis-deafness (KID) syndrome	*GJB2*	−	−	−	+	+ Ker	−	Alopecia	NE	Increased risk for squamous cell carcinoma, hyperkeratotic plaques
MEDNIK syndrome (Mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma syndrome)	*AP1S1*	+	+	+	+	± Cat	−	−	NE	Early lethality, elevated very long chain fatty acids
Multiple sulfatase deficiency	*SUMF1*	+	+	+	−	+ CC	+	−	WMD	Hepatosplenomegaly, gait disturbance, ataxia, neuroregression, course facies, ± ichthyosis
Neutral lipid storage disease with ichthyosis (Chanarin-Dorfman's syndrome)	*CGI-58 (ABHD5)*	±	−	±	+	+ Cat	−	−	NE	Vacuolated leukocytes; myopathy; hepatomegaly, lipid droplets in skin
Refsum's disease	*PHYH, PEX7*	−	−	+	+	+ RP	−	−	NE	Late-onset, ataxia, ± ichthyosis, cardiac conduction defects, lipid droplets in skin
Rhizomelic chondrodysplasia punctata	*PEX7, AGPS, GNPAT*	+	+	±	±	+ Cat	±	−	NE	Ichthyosis 25%, short proximal limbs, failure to

Disorder	Gene Defect	Impaired Cognition	Dysmorphic Facies	Peripheral Neuropathy	Deafness	Eye Abnormality	Seizures	Abnormal Hair	Brain MRI Abnormalities	Associated Clinical Features
										thrive, punctate epiphyseal calcifications, ± ichthyosis
Steroid sulfatase contiguous gene deletion	*STS and contiguous genes*	±	−	−	−	+ RP	+	−	NE	Hypogonadism; short stature
Sjögren-Larsson's syndrome	*ALDH3A2*	+	−	−	−	+Dots, Pp	± (30%)	−	WMD, lipid peaks on MRS	Spastic diplegia > tetraplegia, pruritus
Steroid 5α-reductase type-3 deficiency	*SRD5A3*	+	+	−	−	+ Nyst, Colob, OptN	−	−	Cereb Hypo	Elevated serum transaminases, ± congenital cardiac defects ASD, TGA, pulmonary valve
Trichothiodystrophy with Ichthyosis (Tay's syndrome)	*XPD, XPB, P8/TTDA or TTDN1*	+	−	−	−	+Pp	−	+	WMD, Cereb Hypo	Sparse brittle hair (trichoschisis), ± photosensitivity

ASD, atrial septal defect; Cat, cataracts; CC, corneal cloudiness; Cereb Hypo, cerebellar and/or vermis hypoplasia or atrophy; Colob, coloboma of iris or retina; DCM, dilated cardiomyopathy; Dots, perifoveal glistening white dots; HydroC, hydrocephalus; Ker, keratitis; MRS, magnetic resonance spectroscopy; NE, not established; Nyst, nystagmus; OptN, optic nerve hypoplasia or atrophy; Pp, photophobia; RP, retinitis pigmentosa; TGA, transposition of the great arteries; VEP, visual-evoked potentials; WMD, white matter disease.

*+, indicates a clinical feature is usually present; -, indicates its absence; ±, indicates it has a variable incidence.

Table 2

Diagnostic Approach to Evaluating a Patient with Neuro-Ichthyosis

1. Clinical Evaluations	2. Laboratory Investigations	3. Confirmatory Testing
Genetic evaluation Ophthalmologic exam Audiology evaluation with BAER Brain MRI with MRS EMG/NCV Bone X-rays, as appropriate echocardiogram/ECG, as appropriate	Blood smear for vacuolated leukocytes CK, transaminases Enzyme measurements (lysosomal sulfatases, glucocerebrosidase, fatty aldehyde dehydrogenase) Urine glycosaminoglycans and sulfatides Glycosylated transferrin Skin biopsy for lipid inclusions, histology, and EM Phytanic acid, erythrocyte plasmalogens, very long-chain fatty acids Hair microscopic examination	DNA mutation analysis Comparative genomic hybridization (microarray)

BAER, brainstem auditory-evoked responses; EM, electron microscopy; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; EMG, electromyography; NCV, nerve conduction velocity; ECG, electrocardiogram; CK, creatine kinase.