CHIME SYNDROME (ZUNICH SYNDROME)

Janice Zunich and Nancy Esterly

Indiana University School of Medicine – Northwest, Gary, Indiana, USA (JZ); Medical College of Wisconsin, Milwaukee, Wisconsin, USA (NE)

Introduction

CHIME syndrome is the acronym for a multisystem disorder consisting of **C**oloboma, **H**eart defects, **I**chthyosiform dermatosis, **M**ental retardation, and **E**ar anomalies with hearing loss. Characteristic features of CHIME syndrome include: (1) retinal coloboma; (2) congenital heart defects; (3) migratory ichthyosiform dermatosis at or within a few weeks of birth; (4) moderate to severe mental retardation; (5) seizure disorder exacerbated by high environmental temperatures and fever; (6) ear anomalies and mild to moderate conductive hearing loss secondary to increased desquamation in the auditory canal; (7) genitourinary abnormalities (hydronephrosis, bicornuate uterus); and (8) dysmorphic features consisting of brachycephaly, hypertelorism, broad, flat nasal root, short philtrum, full lips, anomalous dentition, low set, small nipples, brachydactyly, and broad second toes. Additional associated manifestations include feeding difficulties, recurrent respiratory infections in childhood, and large size at birth. Autosomal recessive inheritance is presumed on the basis of recurrence in a sib pair. A molecular basis for the disorder has not been determined.

Historical perspective and eponyms

Initially described in 1983, the first report of CHIME syndrome was that of a young boy with a migratory ichthyosiform eruption, hypertelorism, bilateral retinal colobomata, conductive hearing loss, cleft palate, tooth anomalies, seizure disorder, developmental delay, and large size (Zunich and Kaye 1983). The association of an ichthyosiform dermatosis with retinal colobomata suggested a new neuroectodermal syndrome. The occurrence of congenital heart defects in two additional cases (Zunich and Kaye 1984, Zunich et al. 1988) led to the proposal of the acronym at the 1988 APS/SPR meeting. The occurrence of CHIME syndrome in the younger brother of the index case suggested autosomal recessive inheritance (Zunich et al. 1988). Subsequent case reports have established genitourinary anomalies as a cardinal feature (Shashi et al. 1995, Tinschert et al. 1996, Schnur et al. 1997, Sidbury and Paller 2001). The condition has also been reported as Zunich Neuroectodermal syndrome (Tinschert et al. 1996, OMIM # 280000).

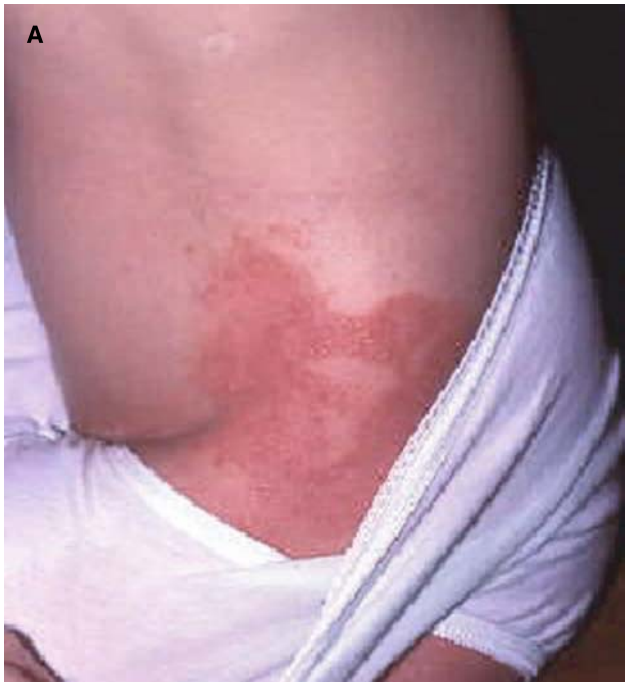
Incidence and prevalence

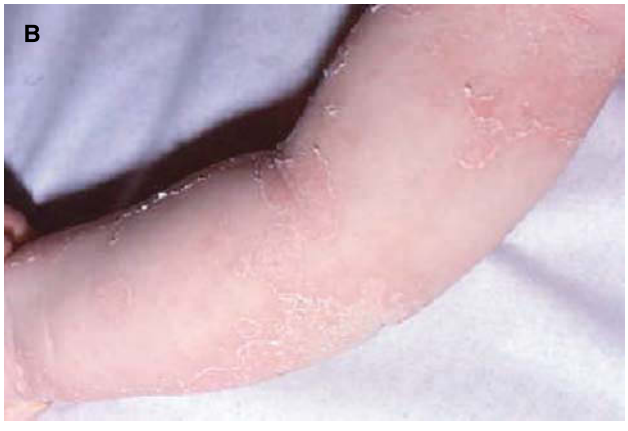
The incidence of CHIME syndrome is unknown. Only 8 cases have been reported in the literature (Zunich and Kaye 1983, 1984; Zunich et al. 1988; Ladda and Zunich 1990; Shashi et al. 1995; Tinschert et al. 1996; Schnur et al. 1997; Sidbury and Paller 2001) with another case unreported (personal communication). A possible tenth case is a male fetus terminated at 21 weeks gestation following ultrasound identification of severe hydronephrosis. Examination identified several craniofacial features consistent with those of his affected sister (personal communication). Excluding the fetus, the female: male ratio of CHIME syndrome is 1.25:1.0.

Clinical manifestations

Skin abnormalities

The onset of the rash is at birth or within the first 4–6 weeks. The cutaneous eruption is migratory and pruritic, characterized by scaling plaques with sharply marginated figurate borders (Fig. 1). In some





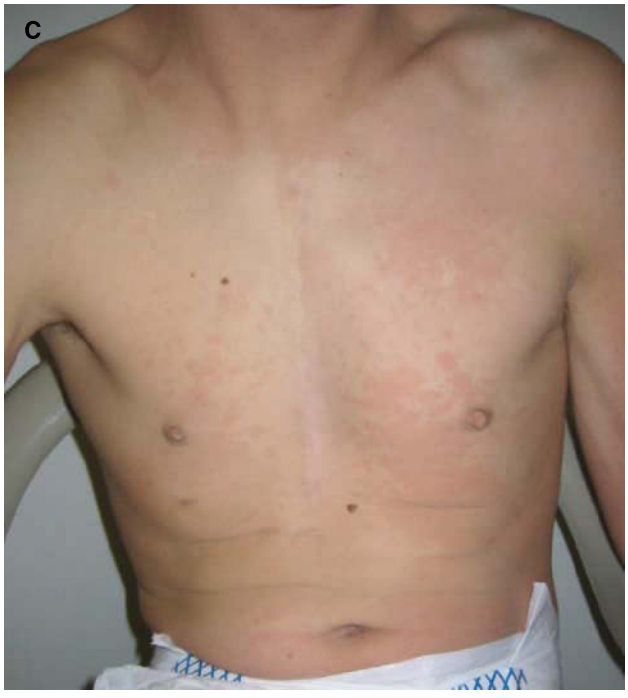


Fig. 1. (**A**–**C**) Cutaneous eruption. Note the figurate border of the plaque. (**B**) Desquamation and erythema.

patients, the rash is psoriasiform while in others it is more ichthyotic. As the rash moves elsewhere, it leaves behind normal skin. There is a lamelliform appearance to the cheeks. The palms and soles are thickened and brightly erythematous with an absence of scales.

Scalp hair, though normal in texture, is fine and somewhat sparse in younger children. Hair is poorly pigmented but seems to darken with age. Eyebrows and eyelashes are normal. Trichorrhexis nodosa has been noted in only one case. In other cases, no abnormalities of the hair shaft were identified. Additional dermatologic abnormalities reported include lipomas (3 cases), dystrophic nails (2 cases), and recurrent skin infections (2 cases).

Histopathologic examination of biopsy specimens from patients show similar changes consisting of disordered keratinization, deep rete pegs in the dermis, and demyelination in the deep dermis.

Nervous system abnormalities

Mild cerebral atrophy has been reported on CT scan or MRI in five cases with mildly enlarged ventricles

(Tinschert et al. 1996) and communicating hydrocephalus (personal communication) noted in single cases. Seizure disorder has occurred in nearly all with onset usually before age 1. Grand mal, petit mal, and myoclonic seizures have all been reported. Abnormal EEG findings were identified in only one of four cases studied (Shashi et al. 1995). High environmental temperatures and fever appear to exacerbate seizures which are often difficult to control.

Moderate to severe psychomotor retardation and especially speech delay are present in nearly all cases. A single child is reported to be only mildly to moderately delayed with a nonverbal IQ of 82 at age 8 (personal communication). Three children are nonverbal and four have only limited language. Receptive language is somewhat better than expressive language skills.

Wide-based gait has been described in all cases. Hypotonia has also been noted infrequently (Ladda and Zunich 1990). Behavior problems are common and include autistic mannerisms and violent behavior towards both oneself and others. Teeth grinding, hitting, and biting have all been reported. In several cases, behaviors have worsened after puberty and seem to be correlated with the degree of discomfort resulting from the rash.

Bilateral retinal colobomata are identified in nearly all cases with choroidal colobomata noted in two individuals (Tinschert et al. 1996, Shashi et al. 1995). Additional, though less frequent, eye findings include myopia, hyperopia, ptosis, heterochromia irides, corneal clouding, esotropia, and exotropia.

All cases have mild to moderate conductive hearing loss, that apparently result from significant desquamation of the auditory canal although one case had abnormal auditory evoked responses. Myringotomy has not been successful in improving hearing.

Craniofacial abnormalities

Characteristic craniofacial features in CHIME syndrome (Table 1) include brachycephaly, fine, sparse hair, hypertelorism, epicanthal folds, flat, broad nasal root and tip, short philtrum, and wide mouth with full lips (Fig. 2). Though head circumference is normal at birth, microcephaly is usually recognized within the

Table 1. Clinical characteristics of CHIME syndrome

Clinical characteristics of CHIME syndrome	Incidence	
	No.	%
Skin and hair		
Migratory ichthyosiform dermatosis	9/9	100
Sparse, fine hair as children	7/7*	100
Thickened palms and soles	5/6*	83
Craniofacial		
Brachycephaly	8/9	89
Hypertelorism	9/9	100
Epicanthal folds	8/9	89
Flat, broad nasal root/tip	9/9	100
Cupped ears, rolled helices	9/9	100
Short philtrum	5/9	55
Full lips	5/9	55
Wide mouth	8/9	89
Anomalies in spacing, size, number of teeth	7/8†	88
Neurologic		
Mental retardation	9/9	100
Seizures	9/9	100
Behavior problems, autistic mannerisms	5/8†	63
Wide-based gait	6/6†	100
Conductive hearing loss	9/9	100
Microcephaly	5/6*	83
Ophthalmologic		
Retinal coloboma	8/9	89
Choroidal coloboma	2/9	22
Myopia, hyperopia	3/9	33
Esotropia, exotropia	2/9	22
Corneal clouding	1/9	11
Cardiac		
Congenital heart defects	7/9	78
Genitourinary		
Hydronephrosis	5/9	55
Renal agenesis	1/9	11
Bicornuate uterus	2/5 females	40
Gastrointestinal		
Feeding difficulties, problems chewing solids	4/9	44
Gastroesophageal reflux	2/9	22

(Continued)

Table 1. (Continued)

Clinical characteristics of CHIME syndrome	Incidence No.	%
Musculoskeletal		
Brachydactyly	7/9	78
Deviation of fingers and toes, clinodactyly	7/9	78
Club foot, joint contractures	4/9	44
Dermatoglyphics		
High percentage of arches	3/4*	75
Recurrent infections in childhood		
Respiratory, sinus	6/9	67
Skin	2/9	22
Miscellaneous		
Broad second toe	8/9	89
Small, low set nipples	5/7*	71
Growth		
Birth weight >90th percentile	3/7*	43
Birth length >90th percentile	4/7*	57

*Not stated in all cases.
†Not able to be evaluated in some cases because of young age or early demise.

first year. The ears have rolled helices and are described in some cases as small, low set, or cupped. The teeth are small and irregularly shaped with increased spacing. Both bifid teeth and extra teeth have been described (3 cases). Infrequently, cleft palate, submucous cleft, and bifid uvula have occurred.

Abnormalities of other systems

Cardiovascular defects have been identified in 70% and include tetralogy of Fallot, transposition, VSD (2 cases), peripheral pulmonic stenosis, subaortic stenosis, and dilated aortic root. While not initially recognized in the first 3 reported cases, genitourinary anomalies have subsequently been noted in all cases and include hydronephrosis (4 cases), unilateral renal agenesis, duplication of the collecting system with ureter entering the vagina, ectopic renal pelvis, bicornuate uterus (2 cases), and cryptorchidism. Menarche has been normal in two females and normal pubertal development has been reported in the four oldest cases (2 males and 2 females).

Though brachydactyly is the most common skeletal abnormality, clinodactyly of the 5th digits

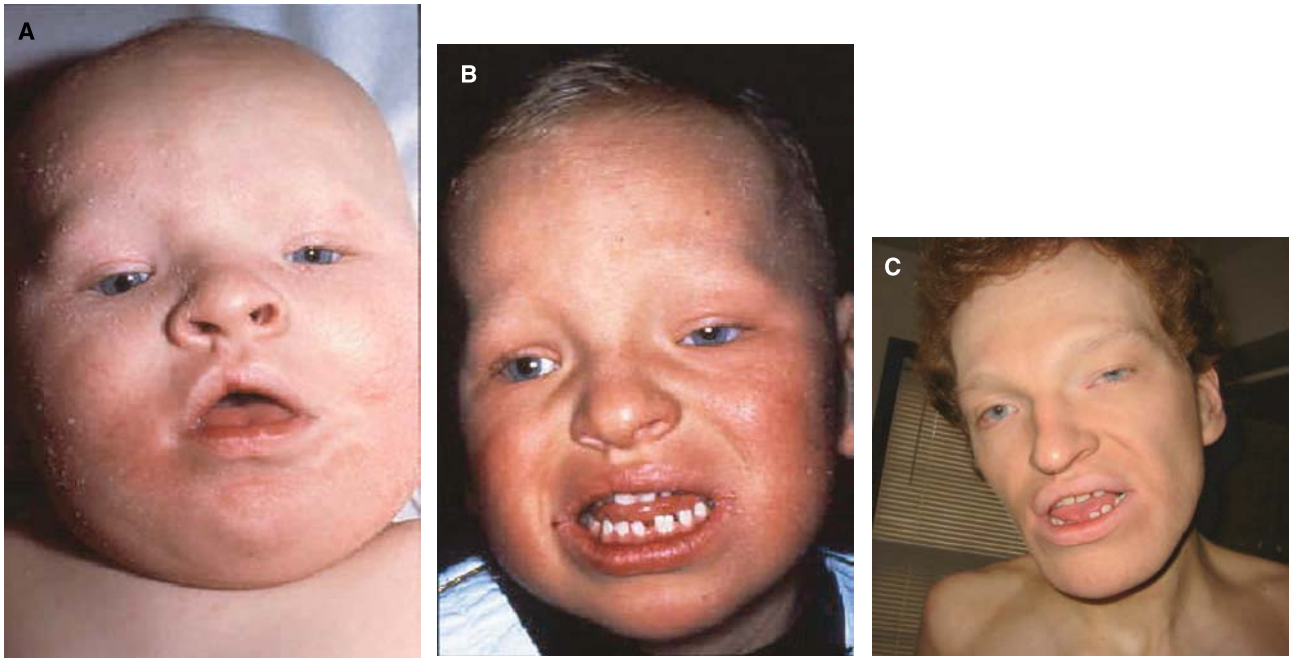


Fig. 2. (**A**–**C**) CHIME syndrome: index case at 1 year, 4 years, and 27 years of age. Note the hypertelorism, epicanthal folds, broad nasal root and tip, short philtrum, full lips, and increased spacing of dentition.

and deviation of the fingers and toes have frequently been present. Deviation of the toes progresses in older individuals, necessitating surgical correction (personal data). Less frequent skeletal features include scoliosis, pectus excavatum, club foot, joint contractures, subluxation of the hip, and dislocation of the radial heads. Coronal craniosynostosis requiring surgery occurred in one case (personal communication).

Feeding problems have occurred in 50% with both difficulty swallowing and chewing solids. Food often needs to be pureed for several years. Rarely, gastrointestinal anomalies have been reported and include gastroesophageal reflux (2 cases), low anal agenesis, hepatomegaly with normal liver biopsy (Schnur et al. 1997), and lymphocytic colitis.

Recurrent respiratory infections in childhood are common. One affected individual died of pneumonia at age 1 (Ladda and Zunich 1990). Recurrent sinus infections have also been noted occasionally (Zunich et al. 1985). No identifiable cause of the recurrent infections has been identified. Immunologic function studies were normal in 2 cases as was a lung biopsy in a single case. One instance of a malignancy was reported in a 4 1/2-year-old girl who developed acute lymphoblastic leukemia (Schnur et al. 1997). The significance of this is not known.

Birth weight and length greater than the 90th percentile have been noted in slightly more than one-third of cases. Bone age was normal in 3 cases. While some affected individuals have demonstrated decreased growth velocity with age (Shashi et al. 1995), others have attained normal heights.

Additional notable features include small, low set nipples and an increased percentage of arches (60–100%) on dermatoglyphics. A common but peculiar finding in 70% of cases is a broad second toe (Fig. 3). On X-ray, this appears to be the result of soft tissue enlargement and not an underlying bony abnormality.

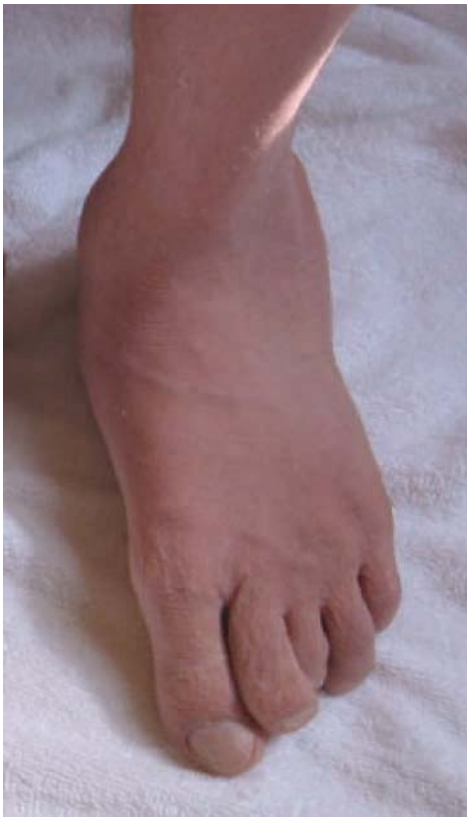


Fig. 3. Note broad second toe and deviation of first and second toes.

Pathogenesis and molecular genetics

The pathogenesis and molecular basis of CHIME syndrome remain elusive. Amino acids, organic acids, and chromosomal analysis including subtelomeres have all been normal. Although initially thought to represent a neuroectodermal syndrome, the major associated features of congenital heart defects and genitourinary anomalies suggest that the condition is truly a multisystem disorder of multiple congenital anomalies/mental retardation resulting from abnormalities of neuroectodermal, mesenchymal and mesodermal derivatives.

Natural history

The ichthyosiform dermatosis can be present at birth or shortly thereafter. Onset of seizures has occurred between 3 weeks and 14 months. Affected individuals seem to have decreased sweating (personal data), possibly complicated by their skin condition, which may be responsible for exacerbation of seizures with high environmental temperatures and

fever. Psychomotor delay is apparent on routine developmental screening in infancy. Although recurrent infections are common in childhood, general health is usually good in older individuals in spite of their associated malformations.

The first 3 reported cases are now 29 (female), 27 and 19 (both males). They require polytherapy for seizure control and management of behaviors and daily skin care. Orthopedic complications including scoliosis, deviation of toes, and hip dysplasia have recently become evident. The female lives in a group home for the developmentally disabled and the males remain with their family.

Management and follow-up

Evaluation of the infant suspected of having CHIME syndrome should include renal ultrasound, echocardiography, and a detailed ophthalmologic examination. Auditory evoked responses to screen for conductive hearing loss is recommended. If normal, repeat hearing evaluations at 9 months and 2 years should be obtained since hearing deficits are so pervasive. Developmental testing at routine intervals beginning in infancy will determine which interventional therapies are necessary. Should seizures develop, EEG and neuroimaging studies would be recommended. In the majority of cases, however, findings on neuroimaging studies have often been nonspecific. Dermatologic evaluation can assist the family in management of the rash. Referral to other medical specialists will be determined by the associated complications of the condition.

Differential diagnosis

The major clinical features of CHIME syndrome readily distinguish it from other ichthyosiform disorders such as KID (Keratitis-Ichthyosis-Deafness) syndrome (Nazzaro et al. 1990) and Refsum disease (Gibberd et al. 1985) in which deafness is neurosensory, not conductive, and intelligence is normal. Although both mental retardation and seizures can be associated with Sjogren-Larsson (Jagell et al. 1981), Netherton (Julius and Keeran 1971), and Rud (Maldonado et al. 1975) syndromes, neither Sjogren-Larsson nor Netherton syndromes has hearing loss. Hearing loss reported in Rud syndrome is neurosensory and not conductive. Punctate keratitis and corneal opacities characterize Sjogren-Larsson syndrome and, rarely, retinitis pigmentosa has been seen in Rud syndrome, but retinal coloboma has not been reported.

CHARGE Association (Blake et al. 1998) and CHIME syndrome share several features: coloboma, heart defects, genitourinary anomalies, and psychomotor delay. Hearing loss is present in both, though neurosensory in CHARGE and not conductive. However, facial features are distinctly different between the two conditions and ichthyosiform skin changes have not been reported in CHARGE.

A newly reported autosomal recessive syndrome with midline brain malformation and mental retardation overlaps some features with CHIME syndrome including coloboma of the eye, heart defects, ichthyosiform dermatosis, ear defects and the nervous system defects (Al-Gazali et al. 2008). However, several features described in CHIME are not present in this newly defined syndrome (Al-Gazali et al. 2008) including deafness, seizures, digedontia, and hair abnormalities.

Treatment

Optimal treatment measures for the eruption have yet to be determined as there is a paucity of patients studied. Caretakers advocate restricted bathing and daily hydrating agents with the use of emollients and keratolytics. Others have advocated frequent bathing. One patient showed modest improvement to isotretinoin (Accutane®). Other therapies, both developmental and medical, will be determined by the clinical extent of involvement and associated complications.

Genetic counseling

CHIME syndrome is presumed to be an autosomal recessive disorder because of the recurrence of the

condition in two brothers. Another affected sib pair is suspected (personal communication, Dr. Anne Turner). The sister was prenatally diagnosed with hydronephrosis at 15 weeks gestation and additionally has retinal colobomata, dilated aortic root, bicornuate uterus, hearing loss, moderate to severe delay, seizure disorder and characteristic dysmorphia. In a subsequent pregnancy, her mother's prenatal ultrasound identified a male fetus with extensive hydronephrosis. The fetus was suspected of being affected and the pregnancy was electively terminated at 21 weeks. Examination of the fetus identified several features consistent with his affected sister, including hypertelorism, overfolded helices, and broad, flat nasal bridge. All other cases have been isolated in families. Nevertheless, because of sibling recurrence, autosomal recessive inheritance needs to be considered a likely possibility with a maximum recurrence risk of 25% for parents of an affected child. Prenatal ultrasound to screen for cardiac or renal malformations may provide presumptive evidence of an affected fetus. In the absence of molecular testing for CHIME syndrome, confirmation of the diagnosis in a fetus would not be possible.

References

Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M (2008) A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family. Am J Med Genet A 146: 813–819.

Blake KD, Davenport SLH, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM (1998) CHARGE association: An update and review for the primary pediatrician. Clin Pediatr 37: 159–174.

Gibberd FB, Billimoria JD, Goldman JM, Clemens ME, Evans R, Whitelaw MN, Retsas S, Sherrat RM (1985) Heredopathia atactica polyneuritiformis: Refsum's disease. Acta Neurol Scand 72: 1–17.

Jagell S, Gustavson K-H, Holmgren G (1981) Sjogren-Larsson syndrome in Sweden. A clinical, genetic, and epidemiological study. Clin Genet 19: 233–256.

Julius CE, Keeran M (1971) Netherton's syndrome in a male. Arch Dermatol 104: 422–424.

Ladda RL, Zunich J (1990) Ichthyosis-coloboma-heart defect-deafness-mental retardation. In: Buyse ML (ed.) Birth Defects Encyclopedia. Cambridge: Blackwell, pp. 945–946.

Maldonado RR, Tamayo L, Carnevale A (1975) Neuroichthyosis with hypogonadism (Rud's syndrome). Int J Dermatol 14: 347–352.

Nazzaro V, Blanchet-Bardon C, Lorette G, Civatte J (1990) Familial occurrence of KID (keratitis, ichthyosis, deafness) syndrome. Case reports of a mother and daughter. J Am Acad Dermatol 23: 385–388.

OMIM^{TM} (2006) Online Mendelian Inheritance in Man. Baltimore: Johns Hopkins University. http://www.ncbi.nlm.nih.gov/omim

Schnur RE, Greenbaum BH, Hewmann WR, Christensen K, Buck AS, Reid CS (1997) Acute lymphoblastic leukemia in a child with the CHIME neuroectodermal dysplasia syndrome. Am J Med Genet 72: 24–29.

Shashi V, Zunich J, Kelly TE, Fryburg JS (1995) Neuroectodermal (CHIME) syndrome: an additional case with long term follow up of all reported cases. J Med Genet 32(6): 465–469.

Sidbury R, Paller AS (2001) What syndrome is this? Pediatr Dermatol 18(3): 252–254.

Tinschert S, Anton-Lamprecht I, Albrecht-Nebe H, Audring H (1996) Zunich neuroectodermal syndrome: migratory ichthyosiform dermatosis, colobomas, and other abnormalities. Pediatr Dermatol 13(5): 363–371.

Zunich J, Kaye CI (1983) New syndrome of congenital ichthyosis with neurologic abnormalities. Am J Med Genet 15: 331–333.

Zunich J, Kaye CI (1984) Letter to the editor: Additional case report of new neuroectodermal syndrome. Am J Med Genet 17: 707–710.

Zunich J, Esterly NB, Holbrook KA, Kaye CI (1985) Congenital migratory ichthyosiform dermatosis with neurologic and ophthalmologic abnormalities. Arch Dermatol 1212: 1149–1156.

Zunich J, Esterly NB, Kaye CI (1988) Autosomal recessive transmission of neuroectodermal syndrome. Arch Dermatol 124: 1188–1189.