MUTATIONS RESPONSIBLE FOR CLINICAL PHENOTYPES OF COLLODION BABIES: AN OVERVIEW

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ABSTRACT
Collodion baby is a descriptive term for infants who are born in a tight shiny membrane (like a plastic wrap) caused by developmental dysfunction in the epidermis. In almost all such cases, different forms of ichthyosiform diseases and the changing phenotypes of ichthyosis (bullous and non-bullous ichthyosis, lamellar and arthropgryphos, self-healing and improving ichthyosis, bathing suit ichthyosis, loricrin keratoderma, trichoodyostrophy, harlequin ichthyosis, ichthyosis vulgaris, ichthyosis vulgariform erythderoderma) are implicated under the influence of different genes (TGM1, ABCA 12, KRT10, CYP4F22, ARCI, loricrin gene) and their mutations (984+1G>A, c.1857delA, c.5653-5655delTAT, 467G.A, ALOXE3, ALOX12, ALOX12B, c.1922_1926+2delGGCTGT, p.Val359Met, G278R, D490G, G278R, c.420A>G, c.832G>A, c.141G>T, P.W47C, p.Arg396His, P.N171Tfs(*)45). To accomplish the target, peer-reviewed English language articles published up to 2016 were selected from Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, comprehensive databases, Cochrane library, Google and yahoo. Literature reports confirm that when membrane cracks the CBs are exposed to a higher risk of complications including loss of fluid, dehydration, instability in body temperature, electrolyte imbalance, morbidity and mortality. Thus they are placed within a chamber of high humidity for gradual sloughing off of the membrane. Besides, regular and symptomatic treatment, identification of genes and their mutations is crucial for gene therapy.

KEYWORDS: colloidal babies, ichthyosiform disease, genes, mutations.

INTRODUCTION
Collodion baby (CB) is a descriptive term for the infants who are born encased in a tight shiny membrane that resembles a plastic wrap or a parchment like membrane covering the entire body surface called the collodion membrane, the membrane is the result of an epidermal cornification and developmental dysfunction. The development of human skin from intrauterine to extra uterine life is interplay of maturing layers and intertwining structures. This transition, involve the issues of premature infant as well as neonatal skin and interruptions due to uterine environment, toxins and developmental errors influenced by genes resulting in disorders of cornification and disruptions in CB skin.

In almost all of the collodion membrane cases, an autosomal recessive ichthyosiform disease is implicated.¹ CB is not a specific disease entity, but is the first expression of some forms of ichthyosis, whose phenotypes are expression of some genes and their mutations. For example, Sharma et al.⁴ reported a CB infant delivered with a lambskin-like membrane encompassing the entire body surface. This was diagnosed to have transglutaminase 1 gene (TGM1 gene) and c.984+1G>A mutation.

In severe conditions, the collodion membrane cracks down and peels over increasing risk of complications, including loss of fluid, dehydration, instability in body temperature, electrolyte imbalance, pneumonia, besides; the risk of getting infections from microorganisms.² Thus they should be placed within a chamber of high humidity for the gradual sloughing off of the membrane and thus monitored for any complications.³ The different ichthyosiform diseases are bullous congenital ichthyosis, non-bullous congenital ichthyosis, congenital...
ichthyosisiform erythroderma, trichothiodystrophy, harlequin ichthyosis, lamellar ichthyosis and arthrogryposis, self-healing collodion ichthyosis, Self-improving collodion ichthyosis, bathing suit ichthyosis, CB with trans-epidermal water loss, CB with heterozygous mutations, CB with hemizygous mutation, CB with loricrin keratoderma, CB with Gaucher disease mutations.  

CB is common phenotype in conditions of some syndromes such as Staphylococcal Scalded Skin Syndrome, Kallman or Conradi-Hunermann syndromes, Sjögren-Larsson syndrome, Vohwinkel syndrome, Netherton syndrome, Shaken baby syndrome pseudo-dysmorphic syndrome.[6-10]

Congenital ichthyosis

Congenital ichthyosis comprises a rare group of monogenic diseases that present at birth as a collodion phenotype or as an ichthyosiform erythroderma, with or without superficial blisters. Depending on which gene mutation causes the disease, the skin problems later in life may range from a severe lamellar or bullous ichthyosis to mild or only focally expressed hyperkeratotic lesions. Recent years have seen advances in recognizing molecular bases of several clinical phenotypes of collodion babies. Furthermore, next-generation sequencing technologies have become powerful tools for the diagnosis of inherited ichthyoses and the discovery of their genetic etiologies, besides; recent advances in understanding of the molecular genetics of ichthyosis have led to several new diagnostic tools that are continuously being updated. Based on this development, and on author’s rich experience in a national genodermatosis center, they described 127 cases of congenital ichthyosis. Applying a combination of phenotypic and genotypic criteria, the patients were classified into groups, such as; Bullous ichthyosis (epidermolytic hyperkeratosis) and related disorders due to keratin mutations, Non-bullous ichthyosiform erythroderma and lamellar ichthyosis mainly due to transglutaminase 1 mutations.  

Inherited Ichthyoses

Ichthyosis is a disorder of keratinization. Inherited ichthyoses are a group of genetic disorders characterized by generalized dry skin, scaling and Hyperkeratosis; these are often associated with erythroderma. These manifestations are due to mutations in genes involved in formation of skin barrier. Inherited ichthyoses consist of ichthyosis syndromes and non-syndromic ichthyoses. Non-syndromic ichthyoses are characterized by the phenotypic expression of the disorder being seen in the skin. It includes ichthyosis vulgaris, recessive X-linked ichthyosis, autosomal recessive congenital ichthyosis, keratinopathic ichthyosis and other forms. Keratinopathic ichthyosis is caused by mutations in keratin genes. Included in autosomal recessive congenital ichthyosis are three major phenotypes (harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosisiform erythroderma) and three of the minor subtypes (self-healing CB, acral self-healing CB and bathing suit ichthyosis). A homozygous missense mutation in CERS3 has been identified in patients with congenital ichthyosis. The condition is characterized by collodion membranes at birth, generalized scaling of the skin and mild erythroderma. It is demonstrated that the mutation inactivates ceramide synthase 3 which is synthesized in skin and testis.  

Lamellar ichthyosis and arthrogryposis

Lamellar ichthyosis is a rare congenital disorder characterized by collodion membrane at birth and facial anomalies (ectropion and ecliplum). Ectropion: The collodion membrane cracks and peels. The tightness of the membrane may cause the eyelids to turn out revealing the pink inner lid, a condition called the ectropion. Ecliplum, is the turning out of the lips due to the tightness of the membrane; it may accompany the ectropion and cause difficulties with nursing. The major underlying genetic defect is in TGM1 with mutations of this gene found in 50% of patients. 

Inherited ichthyosis with pseudoexon activation in the TGM1 gene.

Suga et al.,[15] reported a case of a 12-year-old boy born as a collodion baby with subsequent development of thick scales on his entire body surface. His younger brother showed a similar condition. Arcuate-shaped, large, brownish scales covered his face with ectropion. His lower legs were also covered with larger thick, brownish, plate-like scales, but other areas were covered with smaller scales. Next-generation sequencing for exons and splice sites detected a stop-gain TGM1 mutation leading to p.R71* in transglutaminase 1 (TG1). Another mutation identified was a cryptic mutation in intron 3 that activated a pseudoexon, which was detected by RNA-based analysis of hair bulbs. The deep intrinsic mutation caused another truncation mutation, p.N171Tfs(*)45, in TG1. An in situ TG1 assay demonstrated that TG1 activity was totally lost in this case. The authors concluded that the severe phenotype of the patient developed due to those novel compound heterozygous null truncation mutations in TGM1.

Harlequin-type ichthyosis

Harlequin Ichthyosis (HI) is an extremely rare genetic skin disorder. It is the most severe type of ichthyosis which is characterized by thickened, dry, rough and armor like plates of skin with deep cracks in between. In addition, the eyes, ears, penis, and the appendages are abnormally contracted. Because of the cracked skin, it is easily pregnable by bacteria and other contaminants, which can result in serious risk of fatal infection. Constant care is required to moisturize and protect the skin. It is an autosomal recessive disorder with the majority of affected individuals being homozygous for mutation in the ABCA 12 gene. Affected neonates
usually do not survive beyond first few days of life. [16, 17] In HI, mutations in both ABCA12 gene alleles have a severe impact on protein function and most of the mutations are truncating and cause defective lipid transport. [18] The presence of at least one non-truncating mutation usually causes a less severe congenital ichthyosis (lamellar ichthyosis or congenital ichthyosiform erythroderma). Follmann et al. [19] reported the case of a girl with severe Harlequin ichthyosis. The ultrasound findings showed ectropion, eclairum, deformed nose, hands and feet, joint contractures, hyperechogenic amniotic fluid and polyhydramnion. Sequence analysis of the ABCA12 gene identified two novel mutations, c.1857delA (predicting p.Lys619) in exon 15 and c.5653-5655delTAT (predicting p.1885delTyr) in exon 37, each in heterozygous state. Molecular studies evaluated the mutation (c.5653-5655delTAT) as the disease causing and damaging mutation.

**Bullous congenital ichthyosis**

Bullous congenital ichthyosiform erythroderma is an unusual type of inherited ichthyosis by mutations in the genes that encode K1 and K10. Betloch et al. [20] reported a case of a girl with typical clinical and histopathologic findings of bullous congenital ichthyosiform erythroderma. The girl was found to have a new mutation in KRT10 gene, Glu445Lys at position 445, affecting the 2B region of the KRT10 protein, the end of the rod domain, where many other keratin mutations associated with hereditary skin disease have been reported. This new mutation contributes to add to the catalog of bullous congenital ichthyosiform erythroderma mutations known. In a study on mutation analysis of KRT10 gene in a patient with bullous congenital ichthyosiform erythrodermas, Zhang et al. [21] reported a heterozygous 467G>A mutation in the patient resulting in the substitution of arginine (R) by histidine (H) in codon 156 (R156H) in the IA domain of the KRT10 protein but not in the healthy individuals from the family and the 50 unrelated individuals. The mutation of 467G>A in exon 1 of KRT10 gene identified may play a major role in the pathogenic mechanism of this case of BCIE.

**Non-bullous congenital ichthyosis**

Congenital (non-bullous) ichthyosis is a rare group of keratinizing disorders is sub-classified based on clinical criteria, analysis of TGM 1 gene mutations and electron microscopy of epidermis. Ganemo et al. [22] analyzed three main groups of patients (A) those with transglutaminase 1 gene mutations (B) those without TGM 1 gene mutations showing a coarse, generalized scaling and (C) those without TGM 1 gene mutations showing only fine or focal scaling. Authors concluded that TGM 1 gene mutation is a major cause of congenital ichthyosis in Sweden and Estonia, and is often associated with severe scaling and ultrastructural type II in corneocytes. The transglutaminase-unrelated cases are more heterogeneous, reflecting a more varied etiology.

**Non-Bullous Congenital Ichthyosiform Erythroderma**

The non-bullous congenital ichthyosiform erythroderma is a new form of non-syndromic autosomal recessive congenital ichthyosis. The phenotype usually presents with fine whitish scaling on an erythrodermal background; larger brownish scales are present on the buttocks, neck and legs. A few patients presented a more generalized lamellar ichthyosis. Palmoplantar keratoderm is present in all cases, whereas only 60% of the patients were born as collodion babies. Six homozygous mutations including one nonsense and five missense mutations were identified in a new gene, ichthyin, on chromosome 5q33 in 23 patients from 14 consanguineous families from Algeria, Colombia, Syria and Turkey. Ichthyin encodes a protein with several trans-membrane domains which belongs to a new family of proteins of unknown function localized in the plasma membrane (PFAM: DUF803), with homologies to both transporters and G-protein coupled receptors. This family includes NIPA1, in which a mutation was recently described in a dominant form of spastic paraplegia (SPG6). [23]

**Ichthyosis vulgaris**

Ichthyosis vulgaris is reported to be a post-translational defect in pro-filaggrin expression. It shows fine white flaky scales of the extensor surfaces, trunk, flank, lower legs but spares the folds and wet areas. Bullous congenital ichthyosiform erythroderma is caused by mutations in keratin 1 and/or 10. Autosomal recessive ichthyosis is a term for both lamellar ichthyosis and congenital ichthyosiform erythroderma. They are caused by various mutations in TGM-1 gene. [24]

**Self-Healing Collodion Baby/ Self Improving Collodion Ichthyosis are associated with mutations in genes TGM1 and CYP4F22**

Some collodion babies are born with a tight, shiny cast that sheds in a few weeks. Post shedding, most patients will display features of autosomal recessive congenital ichthyosis (ARCI) later in life but in up to 10% of cases, the skin becomes normal or only minimally involved. This phenotype is called self-healing collodion baby (SHCB), which is considered as ARCI subtype in the classification of congenital ichthyosis. The term self-improving collodion ichthyosis (SICI) has been proposed for these patients. SHCB/SICI was initially associated with mutations in the gene TGM1. However, some cases showing ALOX12B and ALOXE3 gene mutations have also been reported. In a case report, Noguera-Morel et al. [25] reported two cases of SHCB/SICI showing homozygous mutations in the gene CYP4F22. Infants born with ARCI encapsulated in a collodion membrane, shows a lamellar or erythrodermic type of ichthyosis upon shedding. The genotypic spectrum of SHCB patients (11 Swedish and 4 Danish) showed ALOX12B mutations in eight cases, ALOXE3 mutations in three cases, and TGM1 mutations in one case. In three patients, no mutations could be found in any of the known ARCI genes. The authors concluded that
ALOX12B mutations are the leading cause of SICI followed by ALOXE3 mutations. Mazereeuw-Hautier et al. reported spontaneous healing in the ‘self-healing CB’. The authors describe a novel clinical phenotype of acral self-healing CB caused by a new TGM1 mutation. The proband, born to healthy parents, presented at birth as a CB strictly localized to the extremities. The skin condition returned to normal at the age of 3 weeks. The older sister was born as a generalized CB: the condition then developed into lamellar ichthyosis. Molecular analysis of TGM1 revealed three novel mutations in the family. The proband was compound heterozygous for the p.Val359Met and p.Arg396His mutations, whereas the older sister was compound heterozygous for p.Arg396His and a deletion mutation c.1922_1926+2delGGCCGTGT.

Structural modelling of the p. Val359 Met mutation suggested a minor disruption of the protein structure, whereas a modification of protein-protein interaction was predicted for p.Arg396His. These predictions corroborated the analysis of recombinant transglutaminase (TGase)-1 proteins carrying the p.Val359Met and p.Arg396His mutations. Both showed decreased levels of protein expression: p.Val359Met displayed residual activity (12.8%), while p.Arg396His caused a dramatic loss of activity (3.3%). These observations demonstrate for the first time that TGM1 mutations can be associated with acral self-healing collodion baby, and expand the clinical spectrum of TGase-1 deficiency.

Self-healing collodion membrane and mild non-bulloss congenital ichthyosiform erythroderma.

Harting et al. described the clinical and molecular features of 2 cases of self-healing newborns of collodion phenotype developing mild NCIE. A dramatic improvement of the skin was observed in the first few weeks after birth in both cases. The molecular analysis of the ALOX12B gene demonstrated that both patients were compound heterozygous for previously unreported mutations. Both patients were compound heterozygous for novel ALOX12B mutations, underscoring the concept that mutations in at least 2 different genes, ALOX12B and TGM1, may result in this unusual clinical phenotype. Raghunath et al. reported two self-healing collodion baby siblings with markedly diminished epidermal TGM1 activity, the authors found the compound heterozygous transglutaminase 1 mutations G278R and D490G. Molecular modeling and biochemical assays of mutant proteins under elevated hydrostatic pressure concluded significantly reduced activity in G278R and a chelation of water molecules in D490G that locks the mutated enzyme in an inactive Trans conformation in utero. After birth these water molecules are removed and the enzyme is predicted to isomerize back to a partially active cis form, explaining the dramatic improvement of this skin condition.

Bathing suit ichthyosis caused by a TGM1 mutation in a Tunisian child.

Bathing suit ichthyosis (BSI) is an uncommon phenotype classified as a minor variant of ARCI. The phenotype has a unique topography, which involves the trunk, while the face and extremities are spared. Twenty missense mutations have been reported in BSI. Of these 20 missense mutations, nine occurred only in patients with the BSI phenotype and 11 were common to BSI and other types of ARCI. Benmously-Mlika found BSI in a 3-year old Tunisian girl with a mutation of the TGM1 gene. From the age of three months, brownish scaling was noted on the bathing suit area. Histology showed ortho-hyperkeratosis with acanthosis of the epidermis. The granular layer was normal, and the superficial dermis was mildly inflammatory, confirming a diagnosis of proliferating ichthyosis. Molecular analysis in the patient and her parents revealed the mutation I304F of TGM1.

Bathing suit ichthyosis and Self Improving collodion ichthyoses

BSI and SICI are 2 minor variants of generalized autosomal recessive congenital ichthyosis. BSI is characterized by scaling of the skin in a bathing suit pattern, mainly limited to the trunk, whereas SICI is characterized by complete disappearance of the skin lesions. The authors reported genotypic and phenotypic data from a series of 9 patients who were collodion babies and developed BSI or SICI due mutations in TGM1. It was concluded that identical mutations in the same gene shows the possibility of variable evolution of the phenotype of patients.

Collodion baby with Trans-epidermal water Loss (TEWL), and lifelong pronounced scaling.

The TG1-deficient ARCI is a rare and severe genetic skin disease caused by mutations in TGM1. It is characterized by collodion babies at birth, dramatically increased trans-epidermal water loss (TEWL), and lifelong pronounced scaling. The disease has a tremendous burden, including the problem of stigmatisation.

Collodion baby with heterozygous mutations in TGM1 gene

The heterozygous mutations were observed in a Chinese collodion baby. The boy was found to be a compound heterozygote for two novel mutations: c.420A>G (I140M) from his father (occurring in the transglutaminase N domain) and c.832G>A (G278R) from his mother (occurring between transglutaminase N and transglutaminase-like domains).

Both mutations were absent from the control subjects. The boy's condition was caused by two novel compound heterozygous mutations of c.420A>G and c.832G>A of TGM1. Author's results may provide new clues for molecular diagnosis of this disease.
Collodion baby with hemizygous EBP (emopamil binding protein) mutation
A hemizygous EBP mutation in males with a phenotype remarkable for Dandy-Walker malformation, cataracts, cryptorchidism and collodion skin is identified. The family histories were supportive of an X-linked - recessive condition.

CB with Loricrin keratoderma (palmoplantar keratoderma)
Loricrin keratoderma is an autosomal dominant palmoplantar keratoderma heterogeneous in clinical appearance. The authors identified previously reported mutation 730insG in LOR, which elongates loricrin by 22 amino acids because of delayed termination. As pseudoainhums are missing in all patients of the family reported, the authors proposed two compulsory features of loricrin keratoderma: (i) honeycomb palmoplantar keratoderma and (ii) diffuse ichthyosiform dermatosis.

A group of hereditary palmoplantar keratodermas due to heterozygous mutation in the loricrin gene has recently been identified. The authors reported that of five reported pedigrees, four presented as mutilating keratoderma with ichthyosis (variant Voivinkel syndrome), and one as progressive symmetric erythro-keratoderma. The authors reported a new Japanese pedigree of loricrin keratoderma. A 14-year-old male and his 11-year-old female sibling had both been born as collodion babies and were initially diagnosed as having non-bullous congenital ichthyosiform erythroderma, but later developed palmoplantar keratoderma with pseudoinhum. Their father was similarly affected. Direct sequencing of genomic DNA revealed a G residue insertion at codon 230-231 of the loricrin gene. Antibody studies confirmed the presence of mutant loricrin in the retained nuclei. We conclude that loricrin gene mutation may present as congenital ichthyosiform erythroderma, and should be included in the differential diagnosis of collodion baby.

Mutations in Collodion baby with Gaucher disease
Gaucher disease, the most common lysosomal storage disorder, results from the inherited deficiency of the enzyme glucocerebrosidase. Stone et al. performed molecular analyses on a cohort of 31 patients with type 2 Gaucher disease. The cases studied included fetuses presenting prenatally with collodion baby and coyledrops fetalis. Thirty-three of four different mutant alleles out of 62 mutant glucocerebrosidase alleles were found, these included point mutations, splice junction mutations, deletions, fusion alleles and recombinant alleles. Eleven novel mutations were identified in these patients: R131L, H255Q, R285H, S196P, H311R, c.330delA, V398F, F259L, c.533delC, Y304C and A190E. Mutation L444P was found in 25 patient alleles. Seven different sites of recombination were identified. Homozygosity for a recombinant allele was associated with early lethality. The identified mutant glucocerebrosidase alleles include two novel mutations (S196P and R131L) and two rare point mutations (R120W and R257Q), as well as alleles resulting from recombination with the nearby glucocerebrosidase pseudogene. There is significant genotypic heterogeneity in this rare subset of patients with type 2 Gaucher disease. Gaucher disease should be considered in the differential diagnosis of congenital ichthyosis in the newborn period.

CONCLUSION

Literature reports confirm that CB stands at a higher risk of complications, including loss of fluid, dehydration, instability in body temperature, pneumonia and electrolyte imbalance. Thus they should be placed within a chamber of high humidity for the gradual sloughing off of the membrane and thus monitored for any complications. Identification of genes and their mutations responsible for different phenotypes is crucial for gene therapy.

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REFERENCES
11. Vahlquist A, Gänemo A, Pigg M, Virtanen M, Westmark P. The clinical spectrum of congenital...


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