## IN THIS ISSUE…

**Rapid Categorization of Mild Types of Autosomal Recessive Congenital Ichthyosis Undergoing a Phenotypic Shift: Should it be Called "Pleomorphic Ichthyosis" or "Congenital Ichthyosis with Mild Scaling (CIMS)"?**

In this issue of the journal (p. 454–460) Prof. Vahlquist of Uppsala describes a number of ichthyosis entities that initially present either as collodion baby or as congenital ichthyosiform erythroderma and then undergo a phenotypic shift within the first few weeks of life, featuring in later life mostly very mild autosomal recessive congenital ichthyosis (1). In the past, different names have been attached to this clinical phenotype such as "self-improving collodion ichthyosis", the awkward designation "non LI/non CIE congenital ichthyosis", or "congenital ichthyosis with focal scaling". Dr. Vahlquist emphasizes that this clinical phenotype is heterogeneous, like lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE), and points out that, nevertheless, for rapid categorization of the various types of autosomal recessive congenital ichthyosis (ARCI) it would be useful to have a name for it. I fully agree with this idea since in my experience there are quite a number of ichthyosis patients who actually suffer from true ARCI but present with only mild scaling. These patients feature involvement also of the antecubital and popliteal fossae and have a history of much more marked involvement at birth. Often such patients are referred to our outpatient clinic under the diagnosis of "ichthyosis vulgaris" or, if they are boys, under the diagnosis of "recessive X-linked ichthyosis". The prevailing view of many dermatologists is that autosomal recessive congenital ichthyosis has to be very severe, as is the case in LI, or to display marked erythroderma, as is the case in CIE. They are not aware that a considerable proportion of ARCI cases improve quite a bit…

To be frank, although I see the need for a name for this mild type of ARCI that is usually initially rather severe, I find the name "pleomorphic" not to be ideal. "Pleomorphic" implies that it can have many shapes, when in most cases the ichthyosis, in my opinion, does not have manifold different shapes, but simply improves a great deal. Therefore, I would have chosen another name, for example "congenital ichthyosis with mild scaling" (CIMS). In my view, for the dermatologist the learning point is not so much the pleomorphic or multishaped character of the skin lesions, but that the disease starts as a rather severe type of congenital ichthyosis that thereafter improves markedly. It is only KLICK syndrome (2) that undergoes a very remarkable phenotypic shift to a disease state that is no longer reminiscent of the initial presentation. However, I believe that KLICK syndrome is, in this regard, an exception to the rule.

How would "pleomorphic ichthyosis" or, as I would like to call it, "CIMS" fit into the newly established classification of ichthyosis that was discussed in a conference by experts from all over the world last year in Sorèze, France, and that has just been published (3)?

To answer this question, I want to briefly review some of the points of this new classification scheme. A major consensus among the conference participants, of whom Dr. Vahlquist was one, was that even today nosology of ichthyosis should remain clinically based and should a) help clinicians to establish a meaningful clinical diagnosis; b) guide clinicians for the correct genotyping of their patients; and c) facilitate communication with basic science investigators. Keeping in line with previous classifications of ichthyosis (4) the conference decided to keep the distinction between nonsyndromic and syndromic types of ichthyosis. Moreover it was agreed to restrict the term "autosomal recessive congenital ichthyosis" (ARCI) to the group of nonsyndromic types of ichthyosis and to classify harlequin ichthyosis (HI) within the ARCI group.

It is within this newly defined ARCI group where considerable debate took place at the conference and rather conflicting views were expressed. Apart from HI this group also comprises further clinical entities such as LI and CIE. But what about the mild ARCI cases for whom Dr. Vahlquist now suggests the umbrella term "pleomorphic ichthyosis"? In the past some of these have been called "self-healing collodion baby" (5, 6), presenting almost complete clearing of skin lesions. The group of Dr. Vahlquist recently pointed out that a considerable number of these patients actually do not suffer from transglutaminase-1 deficiency but rather from mutations in lipoxygenase genes and created the term "self-improving collodion ichthyosis" (7). It is true that you can hardly refer to a 20-year-old patient as a "baby". Likewise the term harlequin baby has been changed to harlequin ichthyosis.

At the Sorèze conference, Dr. Vahlquist reported on the vast experience of Swedish dermatologists with ARCI cases that usually improve considerably with age. As already discussed above, such cases had often been referred to by awkward names such as "non LI/non CIE" or "congenital ichthyosis with fine or focal scaling (CIFS)" (3). From the German experience I want to state once more that such cases are not rare and in our experience make up 20 to 30% of all ARCI cases. Similar observations have been made in the United Kingdom and France. In particular, such mild cases will come to the attention of medical centres that, in their individual countries, serve as national centres and advise pediatric hospitals and therefore see such patients as neonates in the first two weeks of their life (Fig. 1). This situation is certainly the case in Sweden, Germany and further

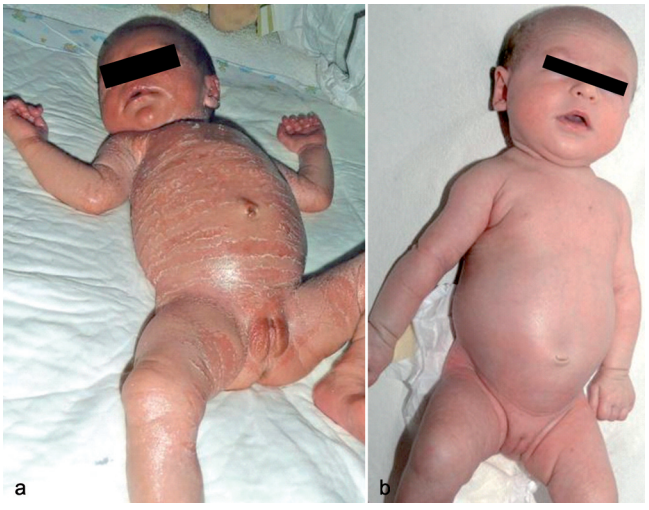


*Fig. 1.* Self-improving collodion ichthyosis as an example of "CIMS" or "pleomorphic ichthyosis". (a) As a neonate at the age of 4 days. (b) At the age of 12 weeks. A mutation has not been identified. Transglutaminase-1 deficiency and lipoxygenase deficiencies have been ruled out in this case.

European countries such as France that have national centres for rare skin diseases.

Despite the actual need for an umbrella term describing mild ARCI cases, this concept was not universally accepted at the conference in Sorèze and therefore did not enter the new classification scheme. There were quite a few colleagues, in particular from North America, who maintained that in their experience such cases are pretty rare. This contrasts with the European experience and one possible explanation that comes to my mind could be that, in the US, patients are not generally referred to pediatric dermatologists as neonates, and once they improve they may no longer be referred at all. Interestingly, colleagues from Japan stated that such mild cases are rather uncommon in their experience too.

In this context, one should consider that the molecular epidemiology of ARCI in Japan and of ARCI in Europe differs considerably. While in Europe mild ARCI cases are often due to lipoxygenase mutations (7, 8), with mutations in the lipoxygenase genes ALOX12B and ALOXE3 together representing the second most common cause of ARCI, explaining about 11% of all German ARCI cases, (8) other types of mutations, such as ABCA12 missense mutations that are associated with severe CIE, are much more common in Japan than in Europe. Next to TGM1 mutations, ABCA12 missense mutations are the predominant cause of ARCI in Japan (9).

Because of such diverse experiences between North America, Japan and Europe, neither the term "CIMS" nor the term "CIFS" managed to become recognized as a clinical phenotype in the new classification scheme and instead we did stay with terms such as "LI/CIE spectrum" (3). Dr. Vahlquist has later coined the new term "pleomorphic ichthyosis", which has not been discussed in the consensus group.

Nevertheless, as pointed out at least in Europe, mild ARCI cases are not uncommon and we are therefore indebted to Dr. Vahlquist that he took the initiative to propose a new term for such cases and to emphasize that, for rapid clinical categorization "pleomorphic ichthyosis" is not the end of the story, but rather should be regarded as an invitation to make a more definite diagnosis such as ichthyosis prematurity syndrome, or KLICK syndrome, or lipoxygenase deficiency, and so on.

So, there is clearly the need for a meaningful new clinical umbrella term, which would take its place next to LI and CIE, to guide clinicians in a fast way to a limited choice of genes that should be typed to achieve a more definite diagnosis. I myself believe in simplicity and therefore would prefer "congenital ichthyosis with mild scaling (CIMS)" as such an umbrella term, but certainly "pleomorphic ichthyosis", which more strongly emphasizes the phenotypic shift some of these diseases undergo, is also a good choice. Very rarely does one see cases that start out as congenital ichthyosis with moderate scaling and then in their lifetime become considerably more severe despite adequate clinical care. For such unfortunate and indeed exceptional clinical cases I see a certain advantage in the term "pleomorphic", which is non-committal and does not imply a marked improvement.

## REFERENCES

1. Vahlquist A. Pleomorphic ichthyosis: A new name for a heterogenous group of congenital ichthyoses characterized by phenotypic shifting and mild residual scaling. Acta Derm Venereol 2010; 90: 454–460.
2. Vahlquist A, Pontén F, Pettersson A.Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK-syndrome): a rare, autosomal recessive disorder of keratohyaline formation? Acta Derm Venereol 1997; 77: 225–227.
3. Oji V, Tadini G, Akiyama M, Bardon CB, Bodemer C, Bourrat E, et al. Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad Dermatol 2010 (in press).
4. Traupe H. The ichthyoses: a guide to clinical diagnosis, genetic counseling and therapy. Springer Verlag, Berlin/Heidelberg/New York, 1989.
5. Frenk E, de Techtermann F. Self-healing collodion baby: evidence for autosomal recessive inheritance. Pediatr Dermatol 1992; 9: 95–97.
6. Raghunath M, Hennies HC, Ahvazi B, Vogel M, Reis A, Steinert PM, Traupe H. Self-healing collodion baby: a dynamic phenotype explained by a particular transglutaminase-1 mutation. J Invest Dermatol 2003; 120; 224–228.
7. Vahlquist A, Bygum A, Gånemo A, Virtanen M, Hellström-Pigg M, Strauss G, et al. Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients. J Invest Dermatol 2010; 13: 438–443.
8. Eckl KM, de Juanes S, Kurtenbach J, Nätebus M, Lugassy J, Oji V, et al. Molecular analysis of 250 patients with autosomal recessive congenital ichthyosis: evidence for mutation hotspots in ALOXE3 and allelic heterogeneity in

ALOX12B. J Invest Dermatol 2009; 129: 1421–1428.
9. Sakai K, Akiyama M, Yanagi T, McMillan JR, Suzuki T, Tsukamoto K, et al. ABCA12 is a major causative gene for non-bullous congenital ichthyosiform erythroderma. J Invest Dermatol 2009; 129: 2306–2309.

*Heiko Traupe*
*Department of Dermatology, University of Muenster,*
*Von-Esmarch-Str. 58, DE-48149 Muenster, Germany.*
*E-mail: traupeh@ukmuenster.de*