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Patient Forum: Building global innovative collaboration for improved quality of life

Diagnosis and Global Albinism Alliance
Antoine Glikson

Collaboration between patients and patient organisations is essential to improve the diagnosis of patients. During this presentation, the Global Albinism Alliance and Genespoir (the French Albinism Association) will be discussed.
Albinism is a disease that causes partial or total hypopigmentation. It affects the skin and eyes. Ocular involvement can be severe.

The Genespoir association was created in 1995 and has 350 to 400 members. Its aim is to promote research into albinism, in particular genetic research.
The year 2007 marked the launch of a collaborative programme to educate clinicians about the molecular diagnosis of albinism. Indeed, although albinism is theoretically diagnosed based on clinical features and molecular findings, in practice, the diagnosis is only primarily clinical. This is due to the fact that few laboratories are capable of testing for the genes responsible for albinism.
Since 2007, two research projects have been set up and financially supported by Genespoir to develop the molecular diagnosis of albinism.
The association's involvement in this project has also enabled patients to be recruited directly from the association's members and indirectly by improving clinicians' knowledge and awareness of molecular diagnostics.
These projects have furthered the knowledge and experience of clinicians and advanced patient education.

The increasing size of the patient cohort is enabling laboratories to gain experience and develop higher-quality tests. In this way, genetic testing is becoming a standard in France and clinicians are learning more about the accessibility of these tests.

The aims of these projects are to:
- Provide access to high-quality genetic tests for patients with albinism in France
- Increase the size of the cohort of albinism patients
- Enable rare forms of albinism to be diagnosed in France

- In 2020: Two new albinism genes were published: OCA8 and HPS11
These partnerships are opening up possibilities in terms of the diagnosis of the disease and the exploration of potential therapies.

Caring for rare skin diseases: Listening, sharing, assisting
Eli Sprecher

It is important to consider the experience of clinicians and that of patients with rare diseases. Patients with rare diseases are often partners in the management of their disease.

Prof Elie Sprecher takes the example of pachyonychia congenita (PC). This genodermatosis is characterised by thickened nails, palmoplantar keratoderma, blisters in areas of friction, oral leukokeratosis, neonatal teeth, and cysts.
This description was passed down by clinicians from generation to generation. PC was then included in the International PC Research Registry. This enabled around 1000 patients to be studied. The analysis of this cohort's data showed that nail dystrophy was not always present and that this disease was associated with high phenotypic variability.
This cohort also showed that plantar pain was the most severe symptom of this disease and could significantly impair walking.

The fascination of describing new rare diseases
John McGrath

Over the past few years, the molecular bases of hereditary skin diseases have been partially explained. Certain discoveries were initially made using genetic linkage analysis and candidate gene approaches.
Genetic linkage analysis approaches typically involve analysing large pedigrees to identify and refine genomic loci that segregate with a specific phenotype, until a specific region containing several candidate genes is small enough to undertake Sanger sequencing with these genes.
For autosomal recessive diseases, another approach consisted of identifying
candidate genes by detecting loss of protein expression or structural differences in skin from a biopsy using techniques such as immunohistochemistry or transmission electron microscopy.
The discovery of new genes stagnated somewhat until the advent of new genome interrogation methods based on next-generation sequencing (NGS). This method led to the discovery of 166 new disease-gene associations for hereditary skin diseases. Of the 166 genodermatoses that were reported, 131 were known disorders with a previously characterised phenotype, while 35 were completely new and had an uncharacterised phenotype.
There was a peak discovery period around 2015, with the use of whole-exome sequencing (WES) which accounted for 90% of discoveries in genodermatoses. There were 63 reported cases of multiple variants, including 13 that exclusively involved genodermatoses and 50 that corresponded to cases of genodermatoses with a non-dermatological Mendelian disorder. The distinct phenotypes are illustrated by the case of a one-year-old boy who had dermatological symptoms consistent with cutis laxa associated with nephrotic syndrome, for which exome sequencing found pathological variants in both PYCR1 and PLCE1. The overlapping of phenotypes is illustrated by the case of homozygous variants in EXPH5 and COL17A1 in a patient with a complex phenotype of epidermolysis bullosa, simultaneously presenting with the clinical features of a simplex form and a junctional form.

The clinical impact of NGS was illustrated through some examples of rare diseases that have been diagnosed:
1. An unexpected cause of hyperpigmentation:

A young girl with unexplained progressive hyperpigmentation with an ABCD4 mutation discovered via WES, whose treatment, based on vitamin B12, resulted in an extremely favourable outcome.
2. An unusual cause of poikiloderma: WES diagnosis of a de novo mutation in the FAM111B gene associated with POIKTMP syndrome (hereditary fibrosing poikiloderma with tendon contractures, myopathy and pulmonary fibrosis).

Epidermolysis bullosa (EB) and skin fragility syndromes

EB classification and diagnosis
Maya El Hachem

EB is a group of mucocutaneous fragility diseases characterised by defective epithelial adhesion caused by the depletion or absence of a specific skin protein.
The deficient protein is responsible for the level of cleavage in the skin. There are four types of EB that are organised according to the cleavage level:
1. Cleavage in basal keratinocytes: EB simplex
2. Cleavage in the lamina lucida of the basement membrane: junctional EB
3. Cleavage below the lamina densa: dystrophic EB
4. Cleavage at multiple levels: Kindler syndrome (KEB)
The different forms of EB are caused by mutations in 16 different genes that code for nine structural proteins belonging to the major adhesion complex of the epidermis, tonofilaments, hemidesmosomes, and anchoring filaments.
They also involve two genes that code for structural focal adhesion proteins (kindlin-1 and integrin subunit alpha 3) as well as two proteins expressed in basal keratinocytes (EXPH5 and KLHL24).

1. EB simplex (KRT5, KRT14 in particular)
The most common form of EB, with onset in childhood. Bullae are clear; they are rarely haemorrhagic. They worsen with increasing temperatures.
There are severe forms of EBS that are mainly autosomal dominant; 50% of these are caused by de novo mutations. Their prognosis is generally good. Immunofluorescence cannot diagnose severe EB, but electron microscopy shows cleavage in basal keratinocytes and aggregated and agglutinated tonofilaments.
There are other forms of EBS:
- EBS-MD: variant in PLEC1
- EBS due to the variant in KLHL24; it is characterised by congenital skin defects of the lower limbs, which heal rapidly, leading to a hypopigmented atrophic lesion. Skin fragility may improve significantly in the first few weeks of life. This form may be associated with dilated cardiomyopathy.

2. Junctional EB
- Severe JEB
This is the most severe subtype of EB; it is generally fatal in the first year of life. It is characterised by extensive erosions particularly affecting the peri-ungual, occipital and periorificial areas.
The lesions progress to granulation tissue that bleeds but does not heal. There are also painful bullae on the oral mucosa.
This form is complicated by airway obstruction with the development of stridor. Patients are at greater risk of sepsis.
- Intermediate JEB
Patients are at increased risk of sepsis in the first few months of life. There is involvement of the oral mucosa, including laryngeal involvement. Nail dystrophy, alopecia and dental anomalies are present.
- JEB with pyloric atresia (ITGB4)

Patients typically present at birth with bullae associated with vomiting and abdominal distension. The outcome is characterised by a decrease in the bullae but the development of uropathy without renal failure.

3. Severe RDEB

It is characterised by severe fragility of the skin and mucous membranes, with widespread erosions and haemorrhagic bullae. There is onychodystrophy or even absence of nails. Other symptoms may be present such as milia, EB naevi, pseudosyndactyly, microstomia, corneal opacity, musculoskeletal contractures, and chronic anaemia.
This form significantly affects quality of life. The main cause of death is squamous cell carcinoma (SCC), with approximately 50% mortality at age 30.

4. Kindler syndrome

Patients present with few bullae, thin skin with nail dystrophy, erythema, photosensitivity, poikiloderma, skin atrophy, pseudosyndactyly, chronic gingivitis and laryngeal and intestinal involvement, sometimes with stenosis. This form is caused by a mutation in the FERMT1 gene.
The disease is diagnosed using various techniques, each of which has its own advantages and disadvantages: immunofluorescence, electron microscopy, and genetic analysis. Rapid diagnosis is essential for optimum management of the child, taking into account the comorbidities associated with each subtype.
It is also necessary in order to offer genetic counselling to families and carry out pre-implantation screening, by chorionic villus biopsy (10 to 12 weeks of gestation) or by amniocentesis (15 to 20 weeks of gestation).

The challenging management of EB neonates

There are around 10 challenges when it comes to managing patients with EB in the neonatal period:

1. Making the correct diagnosis and properly informing the parents
2. Properly treating the wounds and bullae
3. Controlling skin infections and sepsis
4. Treating pain and pruritus, and supplementing with vitamins
5. Managing feeding difficulties
6. Preventing functional complications: syndactyly, contractures, etc.
7. Controlling natraemia: risk of hyponatraemia
8. Monitoring for extra-cutaneous complications: ophthalmological, laryngeal, urological, etc.
9. Never forgetting that the patient is a baby: promoting breastfeeding and the mother-child relationship
10. Conducting therapeutic education with the family

Management of SSC in EB
Jemima Mellerio

Introduction

Squamous cell carcinomas (SCCs) are predominant in patients with recessive dystrophic epidermolysis bullosa (RDEB). They develop early in life. They may be multiple and aggressive and tend to occur in areas with chronic wounds and scars.
They can occur in other types of EB but at a later time (as in Kindler syndrome, and in DDEB and JEB).
A patient with RDEB has a 68% risk of developing an SCC at age 35. The risk of mortality is 87% at age 45. Most patients die within five years of their first SCC.

Clinically, we should be wary of lesions that do not heal, exophytic or hyperkeratotic lesions, and those that appear "different".
Diagnosis is based on a histological assessment.

Staging
A puncture-needle aspiration procedure should be performed on a palpable regional lymph node followed by lymph node dissection if this is positive.
The assessment should be supplemented by a CT scan or MRI if the lymph node is > 5 cm in diameter
and by an FDG-PET/CT scan if it is > 5 cm in diameter and there is suspected dissemination.

Treatment
Surgery is the gold standard but is not always possible with healthy margins. Amputation may be necessary if the lesion is very extensive or if there are anatomical constraints.
Surgery should be combined with lymph node dissection if the lymph node is positive.

Adjuvant treatment
Radiotherapy can be local or regional or performed on distant metastasis.
It is recommended on a small area of skin to avoid side effects.
Conventional chemotherapy: cisplatin or 5-fluorouracil
Generally with little response and a high level of toxicity
Electrochemotherapy: bleomycin given IV
Partial or complete response but painful and risk of sepsis
Other molecules are also used: cetuximab, pembrolizumab, nivolumab, cemiplimab, rigosertib

Potential treatments
Ruxolitinib, omaveloxolone, spliceosome-mediated RNA trans-splicing (SMaRT)

Prevention
Systemic retinoids are generally well tolerated by EB patients. However, there are no clinical studies on their efficacy. There is also no consensus as to when they should be started or whether there is a potential rebound effect.

End-of-life care
Consider palliative care when necessary.

How to/Why diagnose a rare skin disease?
Eli Sprecher

Diagnosing rare diseases is important to be able to explain to patients what they have, better manage their disease, propose treatment and conduct genetic counselling.

Diagnosing the disease
What is the cause of the disease?
Often, clinicians will base their diagnosis on clinical features and histology. However, in some cases, these can be complicated to combine to make the right diagnosis. This is illustrated by the case of a patient concomitantly presenting with clinical features suggestive of Dowling-Degos disease and symptoms of hidradenitis suppurativa. These are not two coexisting diseases but rather but a single disease linked to a mutation in the PSENEN gene.
This is also the case in patients with pachyonychia congenita (PC) linked to a variant in KRT17; 45% of them have a PC phenotype associated with symptoms of hidradenitis suppurativa.

Example of desmoglein in palmoplantar keratoderma (PPK)

Some patients have palmoplantar keratoderma linked to a mutation in DSG1. DSG1 plays a role in keratinocyte differentiation.
Pathological variants in the DSG1 gene reduce the expression of desmoglein-1.
However, other patients who also have a PPK phenotype may have mutations in KLF4 or SERPINA12.
KLF4 plays a role in the activation of DSG1 transcription promoters. In the event of a mutation in KLF4, there will be a decrease in desmoglein-1 transcription. SERPINA12 plays a role in kallikrein-7 which will increase the degradation of desmoglein-1.
These various pathophysiological mechanisms all lead to a decrease in desmoglein in the skin and are useful for developing new therapies.
Another example mentioned in the presentation is the interaction of the ALOXE3 gene (autosomal recessive congenital ichthyosis (ARCI)) and the TGM5 gene responsible for acral skin peeling syndrome. This is illustrated by the case of a family in which the index case had a biallelic mutation in ALOXE3 and TGM5 with an ichthyosis phenotype but no acral peeling skin syndrome phenotype. However, the patient's uncle had a variant in TGM5 and peeling skin syndrome. Would reducing the expression of ALOXE3 eliminate the harmful effect of the TGM5 mutation? This is important for genetic counselling.

Predicting complications

When faced with a phenotype common to several diseases and therefore several genes, it is essential to be able to make a molecular diagnosis in order to be able to manage the specific comorbidities associated with each disease. This concept is illustrated by the differential diagnosis of hypotrichosis, which can be found in diseases linked to mutations in EDAR, CDH3 or GJB2.
Indeed, patients with hypohidrotic ectodermal dysplasia (EDAR) are at risk of hyperthermia, patients with hypotrichosis with macular dystrophy are at risk of blindness, and patients with KID syndrome (GJB2) have an increased risk of cancer.
The three syndromes have very different complications and it is therefore important to know how to distinguish between them to be able to better manage the patient.

Treatment

Knowledge of the biomolecular mechanisms also enables appropriate treatments to be chosen.
This is the case for patients experiencing severe pain related to palmoplantar keratoderma caused by a mutation in KRT16 (PC). Botulinum toxin injections in the bullae cause PPK to significantly improve and also reduce pain.
Treatment with biological agents (TNF-alpha - IL-17 - IL-23) in rare diseases such as Netherton syndrome has also shown real benefits for these patients. However, these diseases are rare and it is therefore difficult to have an adequate design and recommendations for these specific patients.

Complex vascular malformations and tumours

Update of the ISSVA classification
Juan Carlos Lopez

Why update the ISSVA classification? Because the new classification needs to include new genetic and molecular knowledge.
The first notion to discuss is which lesions belong to the group of tumours and which are malformations. Is blue rubber bleb naevus a tumour or a malformation?
Another interesting notion to consider would be whether or not there is a response to sirolimus.
Secondly, regarding the clinical expression of venous malformations, the notions of venous lakes and spongiform and mixed forms should be included.

The presentation also addressed the three phenotypic presentations of capillary malformations. They may have a temporo-cervical segmental presentation (38%); they may involve the shoulder and pectoral area (20% of cases) and the buttocks area (12% of cases).
In conclusion, there has been a significant increase in molecular information relating to vascular anomalies, favouring the development of new gene-based therapies. The classification should take these new concepts into account.

Slow-flow vascular malformations
Olivia Boccara

These include venous and lymphatic malformations. These are benign lesions, for which there is no curative treatment. They should be treated based on the symptoms (no symptoms = no treatment). Treatment should always be in line with the clinical presentation.

Lymphatic malformations (LMs)
- They are disfiguring and painful.
- There is lymphatic stasis that can create oedema and bleeding cysts.
- The aim of treatment is to reduce the volume via compression therapy, sclerotherapy or medication.

Venous malformations (VMs)
- They are also disfiguring.
- They can be complicated by thrombosis and sometimes bleeding.
- They are painful and have a functional impact.
- There is venous stasis that will activate coagulation and generate intra-lesional thrombosis, which will result in inflammation and pain.

This venous stasis can also consume coagulation factors and cause bleeding.
These mechanisms will be responsible for an increase in D-dimers and a decrease in fibrinogen. These are markers of localised intravascular coagulation.

The proposed treatments include compression therapy, sclerotherapy and surgery. Painkillers such as paracetamol, anti-inflammatory drugs such as ibuprofen or anticoagulants (Xa inhibitors) or low-molecular-weight heparin can be added.

The risk of pulmonary embolism
- This is rare, especially with Klippel-Trenaunay syndrome.
- It only occurs in cases of large deep vein anomalies.

Drug treatment
- Sirolimus
- Alpelisib to reduce lymphatic abnormalities: leads to a 20% decrease in mass in 37% of patients.

In conclusion
There has been a significant increase in treatment options; however, none are curative. Each treatment should have an optimal indication. Treatment should not be given if there are no symptoms. Sclerotherapy should be favoured for macrocystic lymphatic malformations and for well-delineated venous malformations.
For lymphatic malformations, surgery (albeit partial in most cases) may be offered in combination with sirolimus.
For venous malformations complicated by coagulopathy (painful or with bleeding), anticoagulants (Xa inhibitors) should be added.
Sirolimus should be proposed for lymphatic malformations and venous malformations if anticoagulants are insufficient or if there is bleeding.
Alpelisib should be proposed if sirolimus is ineffective.

Complex vascular malformations and tumours

Capillary malformations with overgrowth
Andrea Diociaiuti

Vascular malformations are a heterogeneous group of diseases of the circulatory system. They are organised based on the affected vascular structure. They may be isolated or combined or associated with extravascular anomalies.

Capillary malformations (CMs) may be:
- Isolated
- Associated with overgrowth of bones and underlying tissue
- Present in Sturge-Weber syndrome
- Present in PIK3CA-related overgrowth spectrum (PROS)

- Megalencephaly - capillary malformation - polymicrogyria (MCAP)
- Congenital lipomatous overgrowth - vascular malformations - epidermal naevi - scoliosis and skeletal anomalies (CLOVES)
- Klippel-Trenaunay syndrome (KTS)
- Capillary vascular malformation of the lower lip, lymphatic malformation of the face and neck and partial or complete asymmetry or generalised overgrowth (CLAPO)

NGS diagnosis
CMs are caused by mosaic mutations and the frequency of the mutation is usually very low, sometimes in the order of < 1%. Next-generation sequencing is a technique that is sensitive enough to detect these mutations.

Sturge-Weber syndrome
This is caused by an early mutation in the GNAQ gene in the prosencephalon that affects
- the skin of the forehead
- the choroid plexus
- the pia mater
- three patients had leptomeningeal angiomatosis

Mutations in the GNA11 gene can also cause Sturge-Weber syndrome with a bilateral, extensive, reticulate capillary malformation.
GNA11 mosaicism has been identified as being associated with capillary malformations and overgrowth of the lower limbs.

Diffuse capillary malformation with overgrowth (DCMO)
Patients present with diffuse capillary malformations that affect various anatomical sites. These are associated with overgrowth but lack the other typical symptoms to diagnose another PROS syndrome or Sturge-Weber syndrome.
DCMO is due to somatic mutations in PIK3CA and GNA11.
Capillary malformations typically present as pale, reticulated macules without a clear border.
When the patient has a sandal gap or syndactyly, it is most likely due to a mutation in PIK3CA.

CMs with overgrowth
Patients may present with CMs limited to a single anatomical site associated with a proportional overgrowth phenomenon responsible for leg length discrepancy. Patients sometimes present with syndactyly of the toes and less often with a sandal gap.
These abnormalities are associated with somatic mutations in GNAQ or PIK3CA with an allele frequency in tissue of 2-5%. The mutations are undetectable in peripheral blood.

KRAS mutation

Mosaic KRAS variants have been described in various anomalies:
- In epidermal and sebaceous naevi and Schimmelpenning syndrome
- In encephalocraniocutaneous lipomatosis
- In phacomatosis pigmentovascularis
Missense KRAS codon 12 mutations have been associated with
- Arteriovenous malformations of the brain
- Rare slow-flow venous and capillary malformations
The skin is warm when palpated.

Megalencephaly with capillary malformation and polymicrogyria
These patients present with macrocephaly and a combination of trunk, limb and facial overgrowth.
Imaging confirms megalencephaly, which is sometimes associated with thickening of the corpus callosum, a Chiari malformation or hydrocephalus.
The CMs are diffuse and partially reticulated and affect the face in all cases, including the philtrum.
They may also have syndactyly and/or a sandal gap.
Delayed psychomotor development is reported in some cases.
A somatic gain-of-function mutation in PIK3CA is found in all cases (3-21%).

CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal anomalies)
This syndrome combines a capillary-venous and lymphatic malformation of the trunk with urogenital malformations and psychomotor delay.
NGS analysis of the affected tissues shows a recurrent gain-of-function mutation in PIK3CA (allele frequency of 5-46%).

Klippel-Trenaunay syndrome
Combination of a painful capillary-venous and lymphatic malformation, mainly of the lower limb, with leg length discrepancy.
Patients are treated with antiplatelet agents or low-molecular-weight heparin.
Imaging confirms the diagnosis of KTS, showing a complex venous network and a persistent embryonic vein.
NGS analysis shows somatic activating mutations in PIK3CA in the skin (allele frequency of 2.7-6%).

Parkes-Weber syndrome
These patients present with pseudo CMs with a pale halo, overgrowth, and increased local skin temperature.
The lesions are organised in small patches on the trunk and lower limbs.
There is no family history of venous malformations.

In conclusion:
Overgrowth is present in a wide range of capillary malformations. There are some clinical presentations that may point to more specific genes.
There is an overlap between the different diseases that fit in the PROS spectrum.
The phenotypes associated with KRAS mutations need to be better described.
Somatic gene analysis by NGS is essential for making a diagnosis.

Capillary malformations, port-wine birthmarks and other flat cutaneous birthmarks: genotype-phenotype correlation

Ilona Frieden

CMs can affect the face and can also extend over a large part of the body and be associated with overgrowth and asymmetry. They are due to inactivating mutations in GNAQ and GNA11.
They are different from overgrowth associated with mutations in PIK3CA, which are generally progressive with lymphatic, venous and adipose tissue involvement. Here, the capillary malformation

will have clear, geographic edges.
When faced with this type of malformation, we should:
- Verify limb asymmetries
- Perform an MRI
- Investigate lymphatic involvement with the formation of bullae and a risk of infection
- Monitor for the onset of Wilms tumour (for CLOVES syndrome)
- Evaluate the risk of coagulopathy
- Have the patient be monitored by a multidisciplinary team

Bright pink red stains are generally associated with fast-flow vascular malformations. They are flat, with a heterogeneous colour. They may swell and rapidly regain their colour within less than two seconds.
A family history should always be investigated (because they are often autosomal dominant).
Cutis marmorata telangiectatica congenita is a vascular anomaly that presents with a reticulated pattern generally associated with atrophy and ulcers. It generally affects one or two anatomical sites.
Genotype correlation is not well understood.
During the presentation, impressive images of precursors of infantile haemangiomas and tufted angiomas were shown. We noted that venous malformations can sometimes mimic capillary malformations or glomuvenous malformations.
In conclusion, capillary malformations encompass many entities from a genotypic and phenotypic point of view. Some phenotypes overlap with PIK3CA- and GNAQ/11-related syndromes.
Improved genotype-phenotype correlation would enable the classification of capillary malformations to be refined.

Ichthyoses

Congenital ichthyoses are multisystemic diseases
Angela Hernandez Martin

Patients with congenital ichthyosis show cutaneous involvement as well as extra-cutaneous involvement.
There is no systematic evaluation or monitoring for these conditions.
Extra-cutaneous involvement primarily affects:

1. The ears, with the presence of:
- Blockage, conductive hearing loss, hearing loss
- Pruritus, pain, discharge
- Otoscopic findings: desquamation, blockage, etc.

This is more frequent in ARCI, CIE, X-linked ichthyosis.
Hearing loss can lead to learning difficulties and social isolation.
Sometimes the ear may be abnormally shaped, especially in patients with Harlequin ichthyosis, mutations in PNPLA1, or epidermolytic ichthyosis.
Some patients suffer from dysphonia due to thickening of the vocal cords.

2. Ocular involvement
- Eyelid: blepharitis, ectropion, entropion, madarosis
- Cornea: keratitis, keratoconjunctivitis, corneal opacity
- Dry eye syndrome: burning, itching, photophobia.

Early detection of dry eye can prevent corneal damage.

3. Nutritional problems
- Low body weight and short stature as these patients have increased metabolism.

- Low vitamin D levels: especially dark-phototype patients.

Extra-cutaneous involvement is common in congenital ichthyosis.
- Periodic and systematic monitoring are essential.
- Comprehensive patient care programmes with ENT, ophthalmological and nutritional monitoring are needed.

Active research in rare skin diseases

Cutaneous neurofibromas in NF1
Laura Fertitta

NF1 is one of the most common genetic diseases, affecting 1/2500-3000 people.
It is an autosomal dominant disease (NF1 gene (17q11.2), RAS pathway).
It is a multisystem disorder with cutaneous, neurological, ocular and orthopaedic involvement.
Patients also develop benign and malignant tumours. Cutaneous neurofibromas (cNFs) occur in 95% of patients.
NF1 is highly heterogeneous. Over 1400 pathological variants have been described for which no genotype-phenotype correlation has been identified. The clinical consequences of this lack of correlation include, on the one hand, the inability to predict the prognosis/disease severity based on the phenotypes of any family members having the same variant and, on the other, the difficulty of classifying NF1 patients based on the phenotype and optimising their monitoring.

The aim of this study was to develop an empirical classification with the goal of identifying the various subtypes of NF1 to better understand the observed heterogeneity. The groups included in the study did not enable a clinical correlation with a clear aetiological subgroup to be determined, and the cohort analysis showed that the groups overlapped and that animal models were necessary to enhance the data.

Study in murine models
- One hundred percent of mice had developed cNFs after one year.
- Seventy percent of mice developed peripheral nerve tumours.
- Triggers for the development of cNFs included skin wounds and inflammation.

Mice also served as a treatment model: study on the relevance of binimetinib (an MEK inhibitor). The aim was to develop a model to prevent cNF development and evaluate its efficacy in terms of cNF regression.

My personal experience - update on diagnosis and therapy of hereditary (blistering) skin diseases

<u>Laryngo-onycho-cutaneous (LOC) syndrome</u>
- An autosomal recessive EB disease.
- It is a subtype of junctional EB with a mutation in exon 39 of LAMA3 (c.151dup) (specific LAMA3 isoform).
- Most patients come from India or Pakistan.

<u>Clinical presentation</u>
- Patients typically have granulation tissue in the periungual area and on the face that heals very slowly; it is associated with moderate skin fragility and onychodystrophy.
- They have a hoarse voice. They may have laryngeal stenosis which may require a tracheostomy.
- Symblepharon is a pathognomonic symptom.

- These patients also have hypochromic microcytic anaemia requiring iron injections and blood transfusions.

Acral peeling skin syndrome
- This is a subtype of peeling skin syndrome that affects the hands and feet.
- It is an autosomal recessive disease.
- It is characterised by bullae in the superficial epidermis, with pain in the hands and feet and palmoplantar desquamation.
- Pain is the main symptom affecting the quality of life of patients, followed by pruritus and difficulty sleeping.

Skin disease: the challenge of non-coding regions
Elodie Bal

The coding regions of the genome only account for 1% to 2%.
Non-coding regulatory elements are essential for gene expression in specific tissues at specific times. These elements include promoters, enhancers and super-enhancers, silencers and other non-coding RNA.

The role of these non-coding regions was studied through two examples:

Bazex-Dupré-Christol (Bazex) syndrome
The clinical phenotype is characterised by hypotrichosis and hyperhidrosis, follicular atrophoderma and predisposition to basal cell carcinomas (BCCs).
It is an X-linked disease with a high level of intra- and inter-familial variability.
There is loss of ACTRT1 expression in the skin of patients with Bazex syndrome.
The variations are due to enhancers that affect the expression of ACTRT1.

B-cell lymphoma
Active regions of super-enhancers are over-stimulated in B-cell lymphomas.
Recurrent mutations in the intragenic region of BCL2 super-enhancers target the NR3C1 binding site.
NR3C1 codes for a glucocorticoid receptor that can act as a transcription factor. Low NR3C1 expression is associated with a poor prognosis and tumour progression through up-regulation of BCL2.

Non-coding mutations in enhancers and super-enhancers alter gene regulation and expression.
Enhancer mutations interrupt the expression of ACTRT1 in patients with Bazex syndrome.
BCL2 mutations are due to negative regulation by NR3C1 in B-cell lymphomas.
Non-coding mutations are opening up new prospects in the area of genetic diseases via the identification of new signalling pathways.

Training based on clinical case studies

Examples of rare diseases
Ludovic Matin

1. A four-year-old girl with eyelid oedema, without any triggering factors, sometimes associated with swelling of the extremities.

Diagnosis: Hereditary angioedema due to congenital C1 inhibitor deficiency
- Prototype of bradykinin-mediated angioedema
- Severe, non-exceptional, autosomal dominant disorder with 30-50% neo-mutations
- Usually begins in pre-pubertal children but with less characteristic manifestations than in adults

- Recurring abdominal pain
- Diagnostic confirmation via a test measuring C1 inhibitor function (excellent sensitivity and specificity)

Differential diagnosis
- Histamine-mediated angioedema
- Auto-immune disorders
- Systemic disorders including certain connective tissue diseases
- Other hereditary or acquired (drug-induced) bradykinin-mediated angioedemas
- Factitious disorder imposed on another (Munchausen syndrome by proxy)

2. A four-month-old child with a congenital infiltrated copper-coloured plaque on the thigh. The lesion flares up and erythematous papules appear all over the body.
- Histology: immunostaining shows a massive dermal infiltrate of CD117-positive cells.
- Diagnosis: mastocytosis with multiple mastocytomas with a tumour-like presentation, but this presentation is not included in classifications.
- The lesions have spontaneously regressed within a few years.

New vascular disorders
Olivia Boccara

1. A four-year-old girl with a vascular lesion since birth that is gradually growing
Diagnosis: verrucous haemangioma
- The lesions are not always verrucous initially and may become so gradually, which can be confusing.
- The differential diagnosis is microcystic lymphatic malformation.
- The lesion is always limited to the subcutaneous tissue.
- Histology: the lesions are negative for GLUT1 + and D2-40.
- This lesion is linked to a somatic mutation in MAP3K3.

2. A 14-year-old girl with punctate telangiectatic lesions with a small whitish halo around them, associated with diffuse small, pinkish macules.
CM-AVM syndrome
- Type 1: RASA1
- Type 2: EPHB4
- Lower risk of cerebral and spinal AVMs than with RASA1
- Debate: what is the role of cerebral imaging if there are no neurological symptoms?

Diagnosing rare diseases: when clinical findings take precedence: North African experience
Hamida Turki, Nadia Smaili, Asmahène Souissi

1. The presentation focused on images of family cases of epidermolysis bullosa.

2. This was followed by a case of an atypical Orf lesion.

3. Temporoparietal hypotrichosis
- Trichoscopy: black dots (broken hairs), v-sign (broken hairs), flame hairs and hook hairs
- Diagnosis of trichotillomania
- However, the patient also has primary amenorrhoea, ovarian agenesis and uterine atrophy, with facial dysmorphism and hypertelorism
- The hairs have progressed, with miniaturisation and thinning
- Diagnosis of Woodhouse-Sakati syndrome
- Autosomal recessive disease linked to the DCAF17 gene
- Mild and severe forms are correlated with iron accumulation in the brain

- Associated with hearing loss and mental retardation

4. Alopecia has been diagnosed for several years. Sparse eyebrows and no hair in the underarm and pubic areas.
However, there are follicular papules on the face appearing as dermal cysts that are filled with keratin.
The patient has skeletal deformities of the legs related to vitamin D-dependent rickets.
The diagnosis is a mutation in the vitamin D receptor (VDR) gene → Target organ resistance to vit D.
This gene is involved in regulating the hair cycle (apoptosis of the bulb in the catagen phase).
Differential diagnosis: atrichia with papular lesions but vitamin D levels are normal.

5. Hypotrichosis for several months in an 11-month-old child.
Trichoscopy: broken hairs, black dots, exclamation mark hairs, circular hairs
→ Diagnosis of alopecia
Alopecia in infants is rare and is often associated with genetic predisposition.

"Easy" histological diagnosis of rare diseases
Stéphanie Leclerc-Mercier

A seven-year-old boy with facial poikiloderma associated with flare-ups of erythemato-squamous lesions
His father had a FAM111B mutation and died of pancreatic cancer
The patient has POIKTMP syndrome

- Classic appearance of poikiloderma with hyperkeratosis
- But there may be histological changes with lichen planus
- Association with prostate and pancreatic cancers.

A histological examination should be performed in the event of early-onset poikiloderma in young children because the histological findings in POIKTMP are highly characteristic.

Report written by

Dr. Nicolas KLUGER

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Hidradenitis suppurativa and related conditions

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder characterized by the formation of painful lumps under the skin. It often affects intertriginous areas like armpits and groin and affects approximately 4 out 1000 individuals. Syndromic HS belongs to a
subgroup of HS patients disclosing several specific symptoms or conditions together

Table. Examples of syndromic HS

PASH

Pyoderma gangrenosum
Acne
HS
Genetic mutation: CCTG repeats are increased in PSTPIP1 promoter

PAPASH

Pyogenic arthritis + PASH
Genetic mutation: PSTPIP1

PsAPASH

Psoriatic arthritis + PASH
Genetic mutation: unknown

PASS

Pyoderma gangrenosum
Ankylosing spondylitis
HS
Genetic mutation: unknown

Follicular occlusion triad

HS
Acne
Dissecting cellulitis

Follicular occlusion tetrad

HS
Acne
Dissecting cellulitis
Pilonidal sinus

PSTPIP1: proline-serine-threonine phosphatase-interacting protein 1

There are various registries of HS patients, either national or international. The Belgian experience based on the European registry for HS (ERHS) which gather data in a standardized fashion has been reported during the congress. Out of 508 patients with HS, 60% are female, 40% have a familial history of HS, 33% are overweighted/obese, 73% are smoking, diagnosis delay is of 7 years. Regarding comorbidities, 43% suffer from depression, 32% had a past history of severe acne, 7% had an inflammatory bowel disease.
Syndromic HS was rather rare with 2 cases of PASH and one case of PASS. The association between HS and ankylosing spondylitis was more frequent (16 patients). The diagnosis delay was longer for the patients with syndromic HS, about 17 years. HS-associated syndrome should be suspected in case of recurrent episodes of fever, severe joint pain, skin lesion evocative of pyoderma gangrenosum, severe HS and laboratory finding suggestive of systemic inflammation.
Management can be challenging and treatment using biologics such anti-TNF alpha or anti-IL1 provide remissions.

Outcome measures

There is wide number of outcome measures of HS from the original Hurley score (1989) to the more recent HASI-R in 2021.

The Hurley stage is the first score that was developed but it is mainly descriptive of local alteration.

Hurley stage

I

Presence of inflammatory nodules and/or abscesses. No sinus tracts, no scars

II

Presence of inflammatory nodules and/or abcesses
Sinus tracts formations and/or scars

III

Diffuse or near-diffuse involvement across the entire area

The Sartorius score (2003) takes into account the anatomic region involves (axilla, groin, gluteal, or other region, including a distinction between left and right, 3 points per area affected), the number and scores of lesions (abcesses, nodules, fistulas, scars with points per lesion of all regions involved), the longest distance between 2 relevant lesions)< 5 cm, < 10 cm, > 10 cm) and whether all lesions clearly separated by normal skin in each region (yes 0, no 6). The score is quite difficult to use in clinical practice. A modified version was developed to ease its use.

The HS-Physician's global assessment (2012) that staged the disease from clear (0) to very severe (5) according to the number of abscesses, draining fistulas, inflammatory and non-inflammatory nodules. This score is limited by its inability to adapt to severity changes.

The Hidradenitis suppurativa Clinical Response (HiSCR, 2014) used in the studies for adalimumab. HiSCR is met when there is at least a 50% reduction in abscesses and nodules counts count and no increase in abscess count and no increase in draining tunnel count relative to baseline. It is easy to use but has not been validated, lacks of dynamical inclusion of draining tunnels and may not be useful for Hurley III patients with minimal number of abscesses/nodules.

The International Hidradenitis Suppurativa severity Score System (IHS4, 2017) is a continuous score that include the number of nodules, number of abscesses and of draining tunnels. HS is mild is score < 4 points, and severe is >10 points. It is a validated score.

However, there are problems of reliability of the scores between observers, especially when the number of lesions increases. This is explained because counting lesion is time consuming during consultation; single lesions cannot be measured in case of coalescing lesions. Solutions include assessing the body surface area affected, inflammatory induration, open skin surface, inflammatory color change. Thus has been developed recently the HASI-R (HS Area and Severity Index Revised)

What's new in Stevens-Johnson syndrome and toxic epidermal necrolysis?

Mortality of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) between 10 and 40% and sequelae in 90% of the cases. Mortality at 6 weeks is of 23% and at one year 34%
NET is drug induced in 85% of the cases. Known drugs include cotrimoxazole, allopurinol and antiepileptic drugs. Anticancer drugs (checkpoint inhibitors) are a new drug class on the rise for being involved for SJS. However, lichenoid blistering dermatitis associated checkpoint inhibitors are more frequent and may be misdiagnosed as SJS.
It is important to remind that there are cases of epidermal necrolysis (EN) without any medication. The severity is the same as drug induced epidermal necrolysis. Those patients present with a different pro-apoptotic pathway different from drug-induced EN with an overexpression of apoptosis markers such as TWEAK and TRAIL.

Mortality has been traditionally predicted by SCORTEN.

Table 1. SCORTEN

SCORTEN

Mortality (%)

0-1

3.1

2

12.1

3

35.8

4

58.3

>4

90

A new score has been developed a 5-factors scrore (ABCD-10): Age > 50 years, Body surface area > 10% at day 0, Bicarbonates <20mmol/L, underlying C and Dialysis before admission
An Asian team has also reported that the ratio of red cell distribution width (RDW) / hemoglobin was also predictive of in-hospital mortality for patients with SJS/TEN

Management to reduce mortality includes managing acute skin failure, stopping necrolysis, reducing systemic symptoms and promoting healing. Best chance of survival is associated with a management by a team with experience with such condition in a specialized unit. Supportive care in acute phase include heating the room, hydration, pain control, respiratory close monitoring (keeping in mind that laryngeal involvement is predictive of lung involvement), control of infection, nutrition and prevention of anxiety. There is no certainty for systemic treatment as there is a need for randomized controlled studies. There is a big heterogenity according to habits and teams : corticosteroids, intravenous immunoglobulins (IVIg), anti TNF alpha etc.. A recent meta-analysis suggested the association corticosteroids and IVIg could be associated with lower mortality, but other treatments such as cyclosporine alone or with IVIg or IVIg with plasmapheresis and etanercept) are potential effective treatments. Etanercept could be a promising treatment but the modalities of use of etanercept are no so clear.

Rare skin cancer

Skin adnexal carcinomas

M Battistella

Cutaneous adnexal carcinomas are rare, they represent about 0.05% of all sample received in a dermpath laboratory. They are rare but very diverse as illustrated in table 1.

Table 1. Summary of Malignant skin adnexal carcinomas according to the WHO classification 2018 (benign tumors have been excluded)

Tumors with follicular differentiation
Matrical carcinoma (pilomatrix carcinoma)

Proliferating trichilemmal tumor
Trichoblastic carcinoma/carcinosarcoma
Trichilemmal carcinoma
Tumors with sebaceous differentiation
Sebaceous carcinoma
Site-specific tumors
Mammary Paget disease
Extra-mammary Paget disease
Mammary-type anogenital gland adenocarcinoma
Mammary-type anogenital gland phyllod tumor
Tumors with sweat glands differentiation
Microcystic adnexal carcinoma
Porocarcinoma
Malignant mixed tumor
Hidradenocarinoma
Mucinous carcinoma
Digital papillary adenocarcinoma
Adenoid cystic carcinoma
Adnexal adenocarcinoma NOS
Carcinoma arising in spiradenoma, cylindroma or spiradenocyclindroma
Endocrine mucin-producing sweat-gland carcinoma
Squamoid eccrine ductal carcinoma
Syringocystadenocarcinoma papilliferum
Secretory carcinoma
Cribriform carcinoma
Histiocytoid/signet-ring cell carcinoma

Besides, new molecular drivers/rearrengement have been identified allowing to distinguish better adnexal carcinoma subtypes.

According the French database of the CARADERM (Cancers RAres DERMataologiques) network dedicated to rare skin cancers, adnexal carcinomas are mostly of sweat gland origin (50%), followed by follicular differentiation (38%) and sebaceous differentiation (10%). They are mostly located on the head and neck area (>50% of cases), followed by the trunk (13%). Trichoblastic carcinoma is the most frequent type (28%) followed by porocarcinoma (12%) and sebaceous carcinoma and extra-mammary Paget disease (9.7% each). Correct diagnostic can be challenging for pathologists and dermpathologists. Difficulties are the highest with tumors with sweat gland differentiation. All adnexal carcinomas do not exhibit the same risk of local recurrence or metastasis. There is currently a lack of robust data for most of the rare subtypes.
Regarding the clinical care, there is no consensus yet. A safety margin of 5 mm has been suggested along with follow up by clinical (self) examination. However, it is unclear whether some adnexal carcinomas need larger margins > 5 mm, Mohs surgery or sentinel lymph nodes. It seems wise to suggest guidelines by tumor rather than global guidelines that may not suit all the tumors.
Prospective cohort studies with long term behavior, histoprognostic factors, consensus care guidelines and dedicated clinical trials are warranted.

Autoimmune bullous diseases

Bullous pemphigoid: practical challenges and advances in management
Luca Borradori

Bullous pemphigoid (BP) is the most frequent autoimmume subepidermal bullous dermatosis affecting mainly the elderly. It is characterized by subepidermal blistering with a dermal neutrophilic and eosinophilic infiltrate and linear deposits of IgG and/or C3 along the epidermal basal membrane zone. It results from an autoimmune response against BP180 and BP230 hemidesmosomes antigens. The overall incidence is of 10 to 40 cases for 1 million inhibitants per year with and it increase after the age of 70. There is no evidence for a significant association with malignancies or with autoimmune diseases, so screening should be limited to evocative symptoms. On the other hand, there is a known link between BP and neurological and psychiatric disorders (stroke, dementia, Parkinson's disease, multiple sclerosis, epilepsy etc). BP can be also drug-induced (aldosterone antagonists, anticholinergics, dopaminergic medications, gliptins and immune checkpoint inhibitors). The diagnosis is made by direct immunofluorescence associated with detection of circulating antibodies by ELISA tests or indirect immunofluorescence. The classical negative symptoms favoring BP are: absence of atrophic scars, absence of head and neck involvement and absence of mucosal involvement.
The new European guidelines for the management of BP (2022) are soon to be published

Mild or moderate BP

Severe

First lin

Superpotent topical CS twice or once a day on the whole body
Or
Oral CS 0.5 mg/kg/d

Superpotent topical CS twice or once a day on the whol body
Or
Oral CS 0.5 mg/kg/d

CS dependent, relapsing, recalcitrant

Methotrexate, Azathioprine, Mycophenolate mofetil
If moderate BP, doxycycline or dapsone
Rituximab
Intravenous immunoglobulins
Omalizumab
Dupilumab

CS: corticosteroids

Autoimmune bullous skin diseases in neonates and children
Dedee Murrell

In neonates, the most common blistering disease is epidermolysis bullosa. In many cases, one of the parents is known to EB. Consanguineity is a risk factor for such disorder.
Neonatal pemphigus and pemphigoid (BP) are presumably caused by a passive transfer of maternal auto-antibodies across the placenta.

- Neonatal pemphigus displays a stong male predominance, high proportion of premature birth, less mucosal involvement and more extensive skin lesion compared to pemphigus in the adult. It presents are blisters or erosions Pemphigus activity in the mother does not correlated activity in the neonate, but it is more likely to occur if the disease in not under control in pregnancy.

- Childhood pemphigus is very rare. The age of onset is about 8 years. Mucosal involvement is more common than the skin. It can be life-threatening but use of corticosteroids and other immunosuppressants (mycophenolate, azathioprine, dapsone etc) has also side effects. Complete remission without treatment is rare (<20%). Rituximab has been used with some success in children with pemphigus.
- Paraneoplastic pemphigus in children has been observed during Castleman's disease.
- Neonatal BP is usually the consequence of gestational pemphigoid (GP). It affects 5-10% of newborns from mothers with such GP. BP180 antibodies are transferred passively to the fetus. BP is then transient in the neonate and resolves spontaneously in a few weeks.
- Childhood BP is a different condition as it is not related to passive transfert of autoantibodies. Can be triggered by vaccination. Less than a hundred cases have been reported, mostly in after the age of 6 months. Pemphigoid manifests variably with blisters, erosions, vesicles, urticarial plaques, or reticular eruptions
- Cases of severe neonatal Linear IgA bullous dermatosis sometimes with lethal outcomes have been reported while mothers did not have any symptoms nor circulating antibodies. A Japanese team had recently found that there was secretory IgA in the breast milk. By stopping breastfeeding, symptoms improved in the neonate
- Linear IgA bullous dermatosis during childhood affect face, trunks and extremities
- Dermatitis herpetiformis in children is treated by gluten avoidance, dapsone, local corticosteroids and if necessary systemic corticosteroids.

Table. Treatment regimens for autoimmune blistering diseases in childhood

Systemic corticosteroids

Prednisone 0.5-1 mg/kg/day

Dapsone

0.5-2 mg/kg/day

Sulfapyridine

150 mg/kg/day

Colchicine

0.5 mg x 2/day if case of contraindication for dapsone

Azathioprine

1-2.5 mg/kg/day

Rituximab

2-4 doses of 375 mg/m2

Severe drug reactions

DRESS: the Taiwanese experience

Chia-Yu Chu from the National Taiwan University Hospital, in Taipei, Taiwan presented the key features of and his own experience of DRESS (Drug reaction with eosinophilia and systemic symptoms).

- DRESS is an hypersensitivity syndrome which begins acutely within the first 2 months after the initiation of the drug. It presents with infiltrated papules, facial edema or erythroderma/exfoliative dermatitis associated with fever, lymphadenopathy, hypereosinophilia and atypical lymphocytes, and organ involvement such as hepatitis, nephritis, pneumonitis or carditis.
- Facial edema, infiltrated papules, purpuric changes outside of the legs and psoriasiform desquamation are suggestive of DRESS.
- Liver injury is common in DRESS and frequently associated with atypical lymphocytosis. The cholestatic type is the most common type. In less than 10% of the cases, liver injury is present before skin manifestations.
- The most common causes of DRESS include allopurinol, anti-epileptic drugs (such as phenytoin, carbamazepine, lamotrigine), sulfamides, antibiotics and anti-tuberculosis drugs.
- The co-existence of three histopathological patterns (eczematous pattern, interface dermatitis and vascular damage) in a skin specimen is characteristic in DRESS and shows a significant association with clinical severity.
- DRESS is characterized by HHV-6 reactivation. EBV and CMV reactivations seem to be a consequence of the cytokine storms that happen during DRESS.
- The sequelae of DRESS can be divided into 2 major types that appear to occur in different age groups: young patients tend to develop autoimmune diseases, whereas elderly patients are more vulnerable to end-organ failure.
- In case of drug induced exanthema, the combination of fever + eosinophilia + increased liver enzymes or atypical lymphocytes or both) has a 100% positive predictive value of DRESS

Other rare diseases of the skin

Drug repurposing from primary erythromelalgia
Celine Greco

Primary erythromelalgia is an autosomal dominant neuropathy caused by mutations in genes encoding for voltage-gated sodium channels (SCN9A). Its incidence is about 0.36 to 1.1/100 000 person and it is characterized by episodes of pain and erythema on the hands and feet triggered by heat or exercise and improved with cold, rest or elevation. Clinically the patient will present redness, increased local temperature and major burning pain.
Mutations of SCN9A are responsible for a gain of function of nociceptors Nav1.7 that becomes hyperexcitable at subthreshold stimuli. To date there is no approved medication. Various topical anesthetics, oral anti-epileptics, anti-depressant, opioids are usually tried. The impact on quality of life is important due to chronic pain.
In the lack of approved treatments, drug repurposing is the key:

- Topical mepyramine, an antihistamine, can block nociceptor sodium channels. Mepyramine can inhibit Nav1.7 channels mutant. A 20% mepyramin cream (oil in water emulsion) twice a day or as needed allowed a dramatic decrease of pain intensity of erythromelalgia attacks in 12 out of 14 patients from 8/10 to 1/10
- Topical amitriptyline. A 10% cream (oil in water emulsion) twice a day or as needed allowed a reduction of pain intensity from 7.9/10 to 1.9/10 for 8 out 10 patients. The same patients for whom mepyramine was not efficient did not responded to topical amitryptiline
- Systemic cannabidiol at the posology of 1200-1500 mg/d (three times a day) was associated with a reduction of pain from 8.6/10 to 2.8/10 in three months. All stopped opioids, benzodiazepines, anti-epileptics, mexiletine.

Currently Céline Greco acknowledged treating her patients with a combination of oral cannabidiol and a topical treatment (either mepyramine or amitryptiline).

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