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ABSTRACT

New insights in barrier structure of atopic dermatitis

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The formation of an effective epidermal barrier is a main function of the skin. It prevents penetration of harmful substances from the environment like allergens and pollutants and ensures hydration of the skin. The last years have shown that many skin diseases are characterized by defects of the skin barrier, which is localized in the Stratum corneum and consists of protein-rich cells and a lipid-enriched intercellular space. The epidermal barrier requires a regular epidermal differentiation. Atopic dermatitis is a prime example of a skin disorder with defects in epidermal differentiation and epidermal barrier. The skin disease is the result of complex interactions of genetic and environmental factors, which influence the epidermal structure and function, as well as the immune system. The quality of the skin barrier can be assessed by using a new semi-quantitative method to measure intercellular lipid lamellae (lipbarvisR). This procedure was used to evaluate the effect of emollients and also the topical application of drugs like corticosteroids and calcineurin inhibitors on the structure of the epidermal barrier.

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Clinical studies with targeted strategies for atopic dermatitis

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Atopic dermatitis (AD) is a common, chronic inflammatory skin disease with a highly variable

clinical phenotype, heterogeneous pathophysiology and high socioeconomic impact. The pathogenesis of AD includes alterations of the skin barrier and the immune system, which may reflect polymorphisms of immune and barrier genes, as well as triggering factors from the patient's environment. Basic and translational research, as well as clinical trials, has helped broaden our knowledge of the molecular mechanisms underlying the development of atopic dermatitis and to identify potential treatment targets and approaches.

Current topical treatment strategies are mostly based on a combination of emollients with topical corticosteroids, topical calcineurin inhibitors, or UV light. Current choices for systemic treatment are mostly systemic corticosteroids, cyclosporine A, Methotrexate, Azathioprine, Mycophenolate-mofetil.

A number of new agents are currently investigated in phase II and phase III trials, which have a great potential of changing the current treatment paradigms. The functional substance class of Th2 blockers consists of targeted monoclonal antibodies against the Th2 cytokine IL-13 (tralokinumab and lebrikizumab) and the alpha chain of the IL-4/IL-13 receptor (dupilumab). Other pathways under investigation are the itch-mediating axis of the Th2-derived cytokine IL31 and the alpha-chain of the IL31 receptor (nemolizumab); antibodies against the cytokine TSLP; and small molecules inhibiting the CRTH2 receptor and the histamine h4 receptor. Ongoing and recently published clinical trials with these substances will enhance to our knowledge on AD and hopefully result in novel treatment options for our AD patients.

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Genetic Studies in Children

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Genetic studies in children are undertaken with the aim of improving understanding of their conditions, and thus eventually improving health. The process of setting up and conducting such studies however can appear daunting, due to the important requirements of research governance, clinical and technical practicalities, and of course funding. Good planning is essential to take into account issues of consent in childhood, differences in ethnic and cultural groups' perceptions and needs, implications for life insurance, issues surrounding paternity, and alignment of international centres. In the active stage of recruitment, the importance of accurate and in-depth phenotyping is key, as is the technical aspects of the correct choice and handling of samples to allow for the highest quality results. Results must then be dealt with in a safe and professional way, taking into account the setting for delivery of the results to the patient and family, as well as appropriate disclosure of unrelated incidental findings which may have important health implications.

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Expanding clinical and molecular spectrum of phacomatosis pigmentokeratotica

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Phacomatosis pigmentokeratotica (PPK) is characterized by the association of an epidermal sebaceous naevus and a large speckled lentiginous naevus. Associated clinical findings are variably recorded. Postzygotic HRAS and recently BRAF mutations have been found in PPK.

We described a young patient referred to our clinics because of a giant congenital melanocytic naevus (GCMN). Linear verrucous skin lesions were noted on the trunk. She developed seizures at 2 months. MRI showed a focal cortical dysplasia in temporal area. She had a normal psychomotor and growth development. At 15 months, she was treated for a bilateral nephroblastomatosis.

The association of a giant melanocytic naevus, epidermal naevus, neuromelanosis and nephro-

blastomatosis was evocative of PPK. Genetics analyses were conducted on DNA extracted from naevus and nephroblastoma cells. A heterozygous NRAS mutation (c.182A>G/p.Q61R) was found in skin and kidney lesions but not in peripheral blood. No additional mutation was present either in KRAS, HRAS and BRAF.

The postzygotic NRAS mutation present in our patient had earlier been found in patients with GMCN and recently in a patient with Shimmelpenning syndrome. NRAS mutations have never been found in PPK patients. The association of PPK and nephroblastoma is rare and was recorded only once in literature with no molecular data.

Nephroblastoma have been linked to mutations in WT1, WTX and CATNB, leading to overactivation of Wnt/β-catenin pathway. Activating KRAS mutations could act synergistically with Wnt pathway in the development of tumors. Variants of genes involved in Wnt pathway have been found to be more frequent in patients with GCMN. Taken together these data showed that Wnt/β-catenin pathway might play a central role in the development of mosaic Rasopathies.

This report expands spectrum of PPK and suggests the importance of renal follow-up in such patients.

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Preliminary safety results from the French cohort of phase 2a trial of sirolimus in PIK3CA-related overgrowth – the PROMISE study

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Mosaic PIK3CA mutations activating the mTOR pathway result in various tissue overgrowth. Thus, sirolimus is a candidate therapy for PIK3CA-related overgrowth spectrum (PROS). The PROMISE trial (NCT02443818) is an ongoing multicenter (UK, USA and France) non-randomized, open label pilot study to assess efficacy and safety of sirolimus in PROS. The main outcome is alteration in soft tissue volume after 6 months. Patients aged 3 to 65 years with a PIK3CA mosaic mutation and a measurable overgrowth can be enrolled. The primary endpoint is assessed by clinical measurement, photographs, volumetric MRI and dual-energy X-ray absorptiometry (DEXA) scan at baseline (M0), after a 6-month observation period without treatment (M6) and after another 6-month period on sirolimus (M12). Patients are given a daily sirolimus dosage of 0.8 mg per m2 (1-2 mg) for a target plasma level of 2-6 ng/mL. Adverse events are reviewed bimonthly by local and monthly by international safety committees.

From December 2015 to June 2016, 9 children (median age 10.6 years) and 4 adults (median age 26.3 years) were included in the French cohort. As of June 2016, 54 adverse events have been recorded. Nine patients experienced 18 drug-related adverse events (DRAEs). Four had severe DRAE (grade ≥ 3) resulting in definitive withdrawal in 3. DRAEs consisted of 8 infections, 4 thromboembolic or hemorrhagic events, 4 blood test alterations, 1 asymptomatic overdose and 1 case of Still's disease. The mean time interval since treatment initiation at DRAE onset was 34.6 days. DRAEs did not result in trial termination. Efficacy will be assessed once 30 patients in all 3 centers have completed treatment. Despite absence of previous reports of high AE incidence when using sirolimus for vascular malformations, our data raise concern about its safety in PROS patients. Hence, current off-label use of sirolimus in PROS warrants cautious monitoring.

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Disseminated Juvenile Xanthogranuloma – Clinical, diagnostic and therapeutic aspects in 9 children

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To analyze clinical presentations of children with the very rare disseminated juvenile xanthogranuloma (DJXG) as well as diagnostic and therapeutic options with clinical outcome.

Nine children with DJXG were collected at the Dept of Dermatology, LMU Munich and other hospitals in Germany. Answers to a detailed questionnaire including clinical, diagnostic and therapeutic aspects were analyzed and if possible clinical re-examination was performed.

Mean age of onset in 9 patients (5 male/4 female) was 8 months. 4/5 boys had 50 to over 100 papules on the whole body and all girls 7 to 70 lesions mostly on the upper body. One boy had only 3 lesions, however bigger and from birth. Histopathological examination confirmed the diagnostic of JXG in all patients between the age of 2 weeks to 2 years. Abdominal ultrasound examination was performed in 7/9 patients, ophthalmologic examination in 7/9, ECG and echocardiography in 2/9, urine analysis in 2/9, ultrasound of lymph nodes in 1/9, ultrasound of the skin in 1/9 and whole body magnetic resonance imaging in 1/9. All revealed normal results. In 2/9 patients laboratory tests showed increased lymphocytes, eosinophils and GOT. In all patients a wait-and-see strategy was chosen and slow involution of skin lesions was seen in 8/9 patients after several months. In one patient with progressive skin lesions topical treatment with tacrolimus was started without success. Prednisolone pulse therapy every 4 weeks reduced the lesions after 6 cycles.

In 8/9 boys with DJXG 3 times more widespread skin lesions were seen than in girls who had lesions only at the upper part of the body. A larger cohort of patients needs to be investigated in order to detect associations with other diseases, assess the natural course more exactly and give recommendations for its medical management depending of the clinical presentation.

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Scoring infantile haemangiomas – The hemangioma activity score

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Until recently, scoring systems for infantile haemangioma (IH) activity were lacking. We developed the Haemangioma Activity Score (HAS), a simple scoring system for retrospective and prospective use, based on colour, swelling and ulceration. Recently, the Haemangioma Severity Scale (HSS) has also been described.

The following studies were undertaken to validate the HAS and to compare the HAS with the HSS.

We validated the HAS with a retrospective observational study of photographs of IHs. We selected those patients who had clear and representative photographs and had a follow-up of at least six months. To assess agreement, the HAS of these n=78 IHs was scored independently at two time points by three physicians. We calculated the intraclass correlation coefficients (ICC) of the HAS at t=0 and at t=1. In a prospective interventional study with 54 infants with IHs treated with oral propranolol we compared the HAS with the HSS. The HAS and the HSS were applied independently by two observers.

Mean ICC's of three observers of the HAS at t=0 and t=1 were 0.72 and 0.76, respectively.

We noted that HSS scores often remained the same upon improvement of the IH and therefore do not reflect severity. HAS scores decreased over time, with a dramatic drop in the first week of treatment, reflecting the immediate therapeutic responses.

We conclude that the HAS is a promising scoring system for scoring the activity of IHs in pa-

tients at different time intervals. It could be useful in future investigations for examining the activity of IHs after various therapies or for following the natural course. We also conclude that the HAS is to be preferred over the HSS. Advantages: the HAS can also be used in patients with deep IHs and can be used both prospectively with patients and retrospectively on photographs.

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Improved understanding of infant skin physiology, maturation and skin care

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Recent years have seen continuing understanding of skin morphology, physiopathology and function of skin in new-borns and infants, leading to development of age and skin adapted skin care and topical dermatotherapeutic regimens.

For long time pediatric and dermatologic communities did not reach a consensus on what constitutes appropriate skin care practice of newborns and infants, however there is increasing knowledge and advancing evidence-based clinical practice in bathing and cleansing of children, thus improving clinical outcomes.

Functional maturation of newborn skin and functional deficiencies for example in children with skin barrier defects can be objectively determined by measuring Transepidermal water loss, Stratum corneum hydration, ph value, cutaneous elasticity and sebumetry, techniques which provide highly reliable results while used und temperatureand humidity controlled conditions.

European evidence based recommendations on bathing and cleansing of infants have been developed in light of new evidence on skin maturation processes in newborn and infants and randomized controlled clinical trials investigating different aspects of routine care.

Recommendations for infant cleansing, bathing, and nappy care to provide guidance on facial, body and diaper care including the use of emollients have been developed.

Today it can be assumed that bathing is generally superior to washing in new-borns and infants with additonal psychological benefits for the infant and parents. Newborn bathing can be performed without harming the infant, provided basic safety procedures are followed. Water alone or appropriately designed liquid cleansers can be used during bathing without impairing the skin maturation process. Recent publications have even shown that twice weekly use of baby creams and ointments are helpful for maintaining and improving skin barrier function also in healthy children.

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Where stands the Pediatric Dermatology Research Alliance (PeDRA)

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The Pediatric Dermatology Research Alliance (PeDRA) was launched as the research arm of the Society for Pediatric Dermatology (SPD) in 2012 in response to its top strategic priority of advancing research. PeDRA's mission to promote and facilitate high quality and collaborative clinical, translational, educational, and basic science research to help our pediatric patients. PeDRA initially established a governance structure and bylaws. After early SPD support, PeDRA dues (150 members) and revenue primarily from industry fund our initiatives. Almost half of our members serve on PeDRA committees. PeDRA's standalone annual meeting is now in its 4th year of NIH funding, and brings together 120 investigators and collaborators for didactics, discussions, focused working groups, and interaction with representatives from patient support groups and the NIH. Almost all of our members are engaged in the >40 studies through working groups (Inflammatory Skin Disease, Birthmarks, Genetic Disorders, Skin Tumors and Reactions to Cancer Therapies/STARC, and Neonatal Care). To date, 5 have been published or presented at major meetings, including two with European dermatology partners in TREAT and the European Working Group on Pediatric Psoriasis. Our "big" project

will engage the entire PeDRA group and will focus on quantifying the stigma faced by pediatric patients with highly visible skin lesions. This year, PeDRA is providing $85,000 in grant awards for single-site and multi-site studies that support our mission. We actively communicate to the public and members through our website (www.pedra-research.org) and Update Reports. The organization advocates for our patients through sending members and their patients to public forum, as well as letter to the FDA in support of bringing new therapies to our patients. We are also supporting the development of a new guidance document for the FDA on atopic dermatitis studies. Just in its 4th year, PeDRA has made huge strides, and looks forward to partnering with similar alliances globally towards reaching our goals.

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ERN-Skin: a promising network

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The ERN-Skin aims to enhance high-level patient management for rare complex and undiagnosed skin disorders, by improving the: quality, safety, access to highly specialized healthcare. These diseases share : frequent misdiagnosis; lack of training of paramedics; frequent systemic involvement ; poor recognition as a handicap; poor social integration

Objectives: 1.Better exchange of expertise; 2. Improved healthcare organization by pooling the resources; 3.Update/ develop guidelines in cooperation with overlapping ERNs; 4.Improved training of caregivers; 5.Patient/family therapeutic education; 6.Widespread general public information and recognition of the disease as a handicap, 7.Deep phenotyping for a common scientific language; 8.Development of an e-health platform allowing telemedicine and registries (research); 9.Comprehensive socio-economic study.

Methods: 1-Governance thought to ensure maximum geographical and target groups representativity and outreach across the EU; 2.-Subthematic groups (specific clinical outcomes) and transversal groups (deep phenotyping, e-health& registries, training, common clinical outcomes);3-Theoretical and practical courses for specialists and paramedics across the network and other ERNs covering different same symptoms ; 4-Set up of a Patient Representative Council, representing all patient groups; 5-Communication and information: dissemination of Minutes, Reports in/outside the network; development of tools (website, newsletters, etc.); periodic meetings; 6-Support of European scientific societies.

3rd HP relevance: ERN-Skin will facilitate access to better and safer healthcare for citizens by identifying centers with the necessary expertise and resources to treat rare diseases with skin involvement, as well as by sharing knowledge for an improved healthcare offer. ERN-Skin has a strong focus on developing innovative e-health tools for HCPs, thus facilitating cross-border access to expertise for effective patient management.

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Identification of a novel mutation in RIPK4 in a kindred with phenotypic features of both bartsocas-papas and CHAND syndrome

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Three children from an expanded consanguineous Kuwaiti kindred presented with ankyloblepharon, sparse and curly hair and hypoplastic nails, suggestive of CHAND syndrome. To figure out a causal gene, we performed homozygosity mapping, followed by exome sequencing of one affected individual. We initially identified three

homozygous mutations in the linked region, located in the PWP2, MX2 and RIPK4 genes. Recently, mutations in RIPK4 have been reported in Bartsocas-Papas syndrome (BPS) that shows overlapping clinical symptoms with the phenotype observed in the patients studied here. Subsequent analysis showed that mutation c.850G>A (p.Glu284Lys) in the RIPK4 gene was in complete segregation with the disease phenotype. Interestingly, however, our patients did not exhibit cleft lip/palate, a common feature encountered in BPS. Whereas in BPS mutations are located within the serin/threonin kinase of RIPK4, the mutation detected in our family resides just outside of the kinase domain, which could explain the milder phenotype. Our data raise the question if CHAND syndrome indeed is an own entity. Alternatively, CHAND and BPS might be allelic disorders or RIPK4 mutations could confer varying degrees of phenotypic severity, depending on their localization within or outside functionally important domains. Our findings indicate that making an accurate diagnosis based only on the prevailing clinical symptoms is challenging.

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Low 25-hydroxyvitamin D levels in vitiligo. Case report

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Evaluation of serum 25-hydroxyvitamin D levels in patients diagnosed with vitiligo is still controversial, although a significant association has been proved in recent studies, but no correlation with causality or/and prognosis after vitamin D supplementation.

We present a case of a 24-year-old male student, with indoor activities, diagnosed with facial vitiligo at the age of 11. Initially lesions faded during winter time, slight erythema and white small macules being observed around the eyes during summer days. He presented with large vitiligo patches on the face, neck and trunk. Clinical examination confirmed the diagnosis of vitiligo.

Family history for other autoimmune disease was negative. Extended laboratory investigations proved to be within normal limits, no signs of other autoimmune disorder were detected. The serum level of 25-hydroxyvitamin D was 9.4 ng/ml (normal values between 30 and 100 ng/ml). Topical steroids were recommended in combination with nbUVB (311 nm) phototherapy (30 sessions).

No improvement of skin lesion was noticed and the serum level of 25-hydroxyvitamin D remained low. Emollients proved to be less effective to the skin lesions and despite vitamin D supplementation the serum level of 25-hydroxyvitamin D persisted to be low for the following 6 months. The evaluations were made to the same laboratory; repeated endocrine examination did not reveal any abnormality.

No statistical data regarding the serum levels of 25-hydroxyvitamin D within normal population in the same geographical area with our patient exists, thus no conclusions can be made. Presented case is an alarm signal to monitor all vitiligo patients by verifying the serum levels of 25-hydroxyvitamin D at every medical visit and to compare the data within normal population.

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Focal facial dermal dysplasia type 4 – Identification of novel CYP26C1 mutations in unrelated patients

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The Focal Facial Dermal Dysplasias (FFDDs) are a group of rare developmental disorders characterized by congenital scar-like atrophic lesions in the bitemporal (FFDD1, 2 and 3) or preauricular (FFDD4) areas. FFDD4 is characterized by preauricular skin defects without additional dysmorphic findings. Recently, two recessive CYP26C1 mutations were identified in four of five unrelated families with FFDD4. However, since the first report, there has been no study reporting CYP26C1 mutations in FFDD4.

Here we report two unrelated patients with the characteristic manifestations of FFDD4. Four different CYP26C1 mutations were identified including three novel lesions, a missense mutation, c.230G>C (p.Arg77Pro), and two splice-site mutations, c.1191+1G>T (IVS5(+1)G>T) and c.1191+2insT (IVS5(+2)insT). These mutations were not found in the general population, and In silico analyses predicted all three mutations as pathogenic. Compound heterozygosity was validated through parental studies.

These results provide further evidence that CYP26C1 mutations are the molecular genetic basis of FFDD4. CYP26C1 belongs to a family of three mammalian P450 enzymes that are involved in retinoic acid metabolism. Although the precise mechanisms responsible for the atrophic skin lesions caused by the CYP26C1 mutations remain to be elucidated, altered retinoic acid metabolism in the embryonic period is presumably the causative factor.

Identification of additional cases by dermatologists, pediatricians, and family physicians will lead to further understanding of the clinical spectrum of FFDD4 and further define its molecular genetic heterogeneity.

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Endothelial dysfunction in patients with moderate and severe psoriasis without classic cardiovascular predictors

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Chronic plaque psoriasis is chronic inflammatory disease in adults is associated with atherosclerosis and increased risk of cardiovascular diseases (CVD). Endothelial dysfunction represents a key step in the initiation and maintenance of atherosclerosis and may serve as a marker for future risk of cardiovascular events. The aim of our study is to evaluate the presence of endothelial dysfunction (ED) in patients with moderate and severe chronic plaque psoriasis (PS) under 19 years with no clinically evident cardiovascular disease or classic cardiovascular risk factors in order to assess the relationship of disease activity to presence of ED.

Vascular measurements will be performed in accordance with the guidelines for ultrasound evaluation of postocclusive flow-mediated vasodilatation (FMD%) of the brachial artery.

Endothelial dysfunction is manifest even in patients with PS without classic cardiovascular predictors. Identification of cardiovascular risk factors especially in children with chronic inflammatory disease like PS, is important in order to reduce their future risk of cardiovascular events. It is therefore very desirable that this method becomes a standard at the examination of children, with psoriasis as well as juvenile psoriatic arthritis.

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Type 2 segmental PTEN hamartoma syndrome in a 1,5 year old girl

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PTEN hamartoma syndrome (PHS) is an autosomal dominant trait including the Cowden and the Bannayan-Riley Ruvalcaba variant. Type 2 segmental PHS represents a pronounced mosaic manifestation, being superimposed on the non-segmental heterozygous phenotype. It reflects an early postzygotic loss of the corresponding wild-type allele at the PTEN locus, in addition to the germline PTEN mutation. It is very rare and therapy options are limited and only symptomatic.

We report the case of a girl presenting with complex congenital anomalies including dysproportional asymmetric overgrowth, linear epidermal nevus, lipomatosis and vascular changes. A heterozygous PTEN germline mutation (c.798_801+24del; p.?) was found. In addition, the lesional tissue harbored a postzygotic PTEN mutation (c.1003C>T; p.R335*) mosaicism. The father also showed the PTEN germline mutation. Due to very fast growth of tumor mass tumor mass had to be debulked in several steps and a tentative treatment with sirolimus was initiated at the age of 14 months.

Complying with current clinical trials with sirolimus in patients showing "segmental overgrowth syndromes", the dose was adjusted to 0,8 mg/m^2 Body Surface Area (BSA) 2 times daily. As sirolimus treatment had to be interrupted pre- and postoperatively and due to compliance problems, duration of sirolimus therapy has been too short to estimate a long term effect on tumor growth.

Whether a systemic therapy with sirolimus is effective in such pronounced segmental disease and help to improve quality of life in the long term will have to be evaluated.