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Large CMN present many challenges to patients and to the multiple clinicians whose expertise is relevant for their care. Affected patients and their families are confronted with psychosocial difficulties, complex therapeutic decisions, and the risk of neurological problems and malignant degeneration. Multidisciplinary teams are not always possible to convene, requiring particular awareness on behalf of the physician spearheading the management protocol.

The objectives of this second meeting are twofold. On one hand, there has never been a more exciting time for new developments in the physiopathological mechanisms of large CMN onset and development, and implications for the central nervous system. A highly diverse audience of professionals, including dermatologists, plastic surgeons, pediatricians, neurologists, oncologists, cell and developmental biologists, psychologists and geneticists, will exchange the state of the art in current basic and clinical research so as to apply the most current findings in their practice. On the other hand, new patient groups have been emerging on a regular basis since the first meeting, and are seeking models and mentorship. The incipient federation of international advocacy groups will be formalized by a vote of its members on its bylaws and incorporation. The availability and development of patient-managed research resources specific to large CMN and NCM will be reported to the medical and scientific communities.

Discussion and exchanges stimulated by your multiple perspectives as participants will both foster new collaborations and synergize with current ones.

Marseille has an experience dating back millenia in favoring international exchange and cooperation. We extend a warm welcome to you in the very spirit of these, its most cherished traditions.

The Scientific and Steering Committee

Heather Etchevers, Ph.D. - INSERM UMR_S910, Marseille, chair
Jacques Bardot, M.D.- CHU La Timone (Enfants), Marseille
Mark Beckwith - Nevus Outreach, Inc., Bartlesville
Nathalie Degardin, M.D., Ph.D. - CHU La Timone (Enfants), Marseille
Jean-Jacques Grob, M.D., Ph.D. - CHU La Timone, Marseille
Sylvie Hesse, M.D. - CHU La Timone, Marseille
Stéphanie Mallet, M.D. - CHU La Timone, Marseille
Ashfaq Marghoob, M.D. - Memorial Sloan-Kettering Cancer Center, New York
Alain Taïeb, M.D., Ph.D. - CHU Saint André, Bordeaux
Programme
All times include minimum 5 minutes of discussion at the end of each presentation

Saturday, 28 September 2013

9:00-10:30 am  Registration – Patio 1
Refreshments – Salon Frioul

10:30-11:00 am  Welcome addresses – Salon Méditerranée
Alain Taïeb, M.D., Ph.D.
Heather Etchevers, Ph.D.

11:00-11:30 am  Invited speaker
Mark Beckwith, Executive Director, Nevus Outreach, Inc.
Collisions of interest

11:30-12:30 Keynote lecture
Veronica Kinsler, M.D.
The genetics of congenital melanocytic naevus syndrome

12:30-2:00 pm  Lunch – Patio 2 and Terrace
Exhibits

2:00-2:30 pm  Invited speaker – Salon Méditerranée
Ashfaq Marghoob, M.D.
The challenge of managing congenital nevi: remove or not remove?

2:30-3:00 pm  Invited speaker
Josep Malvehy, M.D.
The congenital melanocytic nevus registry in Catalonia: results of a multidisciplinary network of centers

3:00-3:20 pm  Harper Price, M.D.
Application of revised criteria for classification of congenital melanocytic nevi in a selected population

3:20-3:50 pm  Invited speaker
Luc Thomas, M.D., Ph.D.
Congenital nevi of the nail unit: the International Dermoscopy Society (IDS) register experience

3:50-4:20 pm  Refreshments – Salon Frioul
Exhibits

4:20-4:40 pm  Celine Eggen, M.D. – Salon Méditerranée
Current practice in the treatment of congenital melanocytic naevi: a survey among clinicians in the Netherlands

4:40-5:00 pm  Pierre Moullot, M.D.
Neurofibromatosis and large congenital melanocytic naevi

5:00-5:20 pm  Géraldine Jeudy, M.D.
Phacomatosis pigmentosa multiplex: long term follow-up in an adult patient

5:20-5:40 pm  Sven Krengel, M.D.
Congenital melanocytic nevi with features of speckled lentiginous nevi

5:40-6:10 pm  Invited speaker
Alain Taïeb, M.D., Ph.D.
The giant nevus syndrome and phacomatosis pigmentokeratotica: the enlarging spectrum of mosaic pigment cell RASopathies
**Sunday, 29 September 2013**

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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| 9:00-9:30 am     | Invited speaker – Salon Méditerranée  
Harper Price, M.D.  
*CMN and the experience of itch: a snapshot of an ongoing patient based survey* |
| 9:30-10:00 am    | Invited speaker  
Miguel Reyes-Múgica, M.D.  
*The pathology of congenital melanocytic nevi and neurocutaneous melanocytosis* |
| 10:00-10:30 am   | Invited speaker  
Sylvie Fraitag, M.D.  
*Malignant melanoma occurring in patients with a large congenital melanocytic nevus: retrospective study of 10 cases* |
| 10:30-11:00 am   | Refreshments – Salon Frioul  
Exhibits |
| 11:00-11:20 am   | Sven Krengel, M.D. – Salon Méditerranée  
*Case reports of melanoma in children and adolescents - a systematic analysis of the literature* |
| 11:20-11:40 am   | Regula Waelchli, M.D.  
*Neurological abnormalities in children with congenital melanocytic naevi - a prospective 25 year study* |
| 11:40-12:00      | Guillaume Captier, M.D., Ph.D.  
*Neurocutaneous melanocytosis associated with a large congenital melanocytic nevus: treatment and follow-up of one case* |
| 12:00-12:20 pm   | Heidi Küsters-Vandevelde, M.D.  
*Primary melanoma of the CNS in children is driven by congenital expression of oncogenic NRAS in melanocytes* |
| 12:20-12:50 pm   | Invited speaker  
Yasmin Khakoo, M.D.  
*Neurocutaneous melanocytosis: targets for treatment* |
| 12:50-2:15 pm    | Lunch – Patio 2 and Terrace  
Exhibits  
Worldwide CMN Registry Working Group meeting, 1:30 pm – Salon Raimu |
| 2:15-3:15 pm     | Plenary lecture – Salon Méditerranée  
Bruce Bauer, M.D.  
*Surgical management of large and giant nevi: the role of tissue expansion in the “current state of the art”* |
| 3:15-5:40 pm     | Patient association breakout meeting – Salon Raimu |
| 3:15-3:35 pm     | Anissa Belkhou, M.D.  
*Skin expansion for congenital melanocytic nevi in children: our experience from 1990-2009* |
| 3:35-4:00 pm     | Alexander Margulis, M.D.  
*Treatment of congenital pigmented nevi with tissue expansion based on our experience with 163 patients over ten years* |
| 4:00-4:30 pm     | Refreshments – Salon Frioul  
Exhibits |
| 4:30-4:50 pm     | Isabelle James, M.D. – Salon Méditerranée  
*Management of giant naevi of the face; review of 44 cases treated by full thickness skin graft, in one stage or after expansion* |
4:50-5:10 pm  Clemens Schiestl, M.D.
*Face the challenge – the Zürich approach of reconstructive surgery for facial CMN*

5:10-5:40 pm  Invited speaker
Nathalie Degardin, M.D., Ph.D.
*The surgical arsenal in large congenital melanocytic nevi*

5:40-6:15 pm  Invited speaker
Ornella Masnari, Ph.D.
*Psychological aspects of congenital melanocytic nevi*

6:30-7:00 pm  The following with a ticket to the Gala Dinner:
Welcome to the Union Nautique Marseillaise (U.N.M.)
On the far side of the Vieux Port – a 25 minute walk from the conference

7:00-8:00 pm  Big Band 13 Orchestra and cocktail reception

8:00-11:00 pm  Buffet dinner catered of Provençal specialties

**Monday, 30 September 2013**

8:30-8:50 am  Invited speaker – Salon Méditerranée
Heather Etchevers, Ph.D.
*Animal models for CMN, NCM and related conditions: pros and cons*

8:50-9:20 am  Invited speaker
Lionel Larue, Ph.D.
*What about a mouse model for the congenital giant naevus?*

9:20-9:40 am  Sarah Guégan, M.D.
*Characterization of initiating cells in large congenital melanocytic nevus*

9:40-10:00 am  Sophie Böttcher, M.D.
*Restoring original donor skin colour by addition of melanocytes to skin substitutes*

10:00-10:30 am  Refreshments – Salon Frioul

10:30-10:50 am  Bernhard Wehrle-Haller, Ph.D. – Salon Méditerranée
*Tethered Kit-ligand/c-kit-mediated niche anchorage and signaling is kinase-independent and imatinib-insensitive*

10:50-11:10 am  Randi B. Silver, Ph.D.
*Role of mast cells in scar formation*

11:10-11:30 am  Miguel Reyes-Múgica, M.D.
*Mast cells are increased in skin of patients with giant congenital melanocytic nevi*

11:30-12:30 am  Keynote lecture
Alain Verloes, M.D., Ph.D.
*RASopathies: the spectrum of constitutional disorders of RAS/MAPK activation*

12:30-1:00 pm  Nicolas Lévy, M.D., Ph.D. - Director, Fondation des Maladies Rares, France
*Naevus Global - international federation of CMN patient associations*

**Closing Remarks**
Collisions of Interest
Mark Beckwith
Nevus Outreach, Inc., Bartlesville, Oklahoma, USA

At scientific meetings, we are cautious to avoid even the appearance of having conflicts of interest. But, to paraphrase Dr. Ilona Frieden, sometimes if one has no conflicts, it is possible one may have no interest. Patients with large congenital melanocytic nevi (LCMN) or neurocutaneous melanocytosis (NCM) carry a burden they did nothing to deserve, and these diseases are major challenges to their daily lives. This is a life-conflict that gives some families an overwhelming interest in finding solutions. As co-Founder and CEO of Nevus Outreach, a large patient association for people affected by LCMN and NCM, I will use our organization’s recently-completed 2013 Oklahoma Freewheel Grassroots Fundraiser to demonstrate how patient associations play a key role in society and improve the lives of people with LCMN and NCM. I will bring those in attendance up to date on the continuing efforts to build Naevus Global, a new world-wide umbrella organization under which LCMN patient associations all over the world will work together to achieve their common goals. Included will be a discussion of the new Global LCMN Registry commissioned by the patient associations at the 2011 International Expert Meeting on LCMN and NCM in Tübingen, Germany. Where there is interest, there will be conflicts. Interest is vitally necessary; conflict is inevitable. This will not stop the patient associations. On the contrary, it will spur them forward.

Notes:
The genetics of congenital melanocytic naevus syndrome
Veronica Kinsler
UCL Institute of Child Health and Great Ormond St Hospital for Children, London, UK

The genetic basis of congenital melanocytic naevus syndrome has recently been found to be a post-zygotic activating mutation in the oncogene NRAS. As part of this finding is a new aetiological understanding of the increased risk of malignant melanoma in this condition. The work leading up to these findings will be reviewed, and the implications for current clinical management and future therapies discussed.

Notes:
The challenge of managing congenital nevi: remove or not remove?

Ashfaq Marghoob

Memorial Sloan Kettering Cancer Center, New York, USA

Many physicians advocate for the excision of all congenital melanocytic nevi (CMN) believing that it reduces the risk of developing melanoma. However, mounting scientific evidence is forcing us to question this practice. While the main impetus for prophylactic excision stems from the knowledge that the relative risk for developing melanoma is high, apathy towards surgery stems from the knowledge that the absolute risk is quite low. Other factors deterring physicians from selecting surgical options include the lack of evidence that removal of CMN actually lowers melanoma risk and that the aesthetic / functional outcomes are often less than desirable. The potential pros, cons, risks, and benefits of excision must be weighed against each other for each individual patient prior to recommending surgery or steering them away from surgery. In essence, each CMN patient requires a management plan tailored towards the individual based on the size, thickness, and location of the CMN, and based on its potential psychosocial impact. For patients opting for surgical intervention, the treatment should attempt to reduce risk of developing cutaneous melanoma while simultaneously optimizing the aesthetic and functional outcomes. In addition, issues such as the risk of surgery, anaesthesia, and scarring should be disclosed and it is imperative that realistic expectations be set from the start. In addition, clinical follow is often recommended for many of these patients. This will require attention to methods of optimizing the clinical follow-up examination including determining the value of clinical inspection, palpation, dermoscopy, and/or other imaging modalities. Psychosocial support together with attention focused on providing ways of concealing cosmetically sensitive CMN or scars may prove beneficial. Lastly, some individuals with CMN are at increased risk for developing neurocutaneous melanocytosis. Following these individuals for the development of signs and symptoms suggestive of CNS involvement also needs to be taken into consideration.

Notes:
The congenital melanocytic nevus registry in Catalonia: results of a multidisciplinary network of centers
Josep Malvehy
Dermatological Diagnosis Centre (CEDILP), Barcelona, Spain

Catalonia is a region located in the north-eastern part of Spain, with a population of 7 million inhabitants. In 2000, a network of melanoma centres was created for a registry, production of common clinical guidelines, collaborative research, second opinions in complex cases and management of patients with melanoma. In this project, 23 hospitals of the territory joined in a registry that facilitates the collection of epidemiological data about these patients. In addition, a registry of complex congenital melanocytic nevi was established in 2012. A Steering Committee populated by dermatologists, plastic surgeons, paediatricians, pathologists, radiologists, medical oncologists, psychologists and research nurses, worked out guidelines and protocols for the management of children with this disease.

A digital platform for the registry and efficient communication of the cases and discussion of patients among centres was created in 2012 to facilitate fast clinical decision-making in large congenital nevi and derivation of patients to referral centres when needed. This model will be evaluated yearly and exported with the use of a multilingual version of the digital application available for other groups in Europe and Latin America.

Notes:
Application of revised criteria for classification of congenital melanocytic nevi in a selected population

Harper N. Price*, Sven Krengel, Judith O’Haver, Kellie Badger, Heather Etchevers, Steve Dusza, Ashfaq Marghoob
Phoenix Children’s Hospital, Department of Dermatology (HNP, JO’H, KB), Phoenix, AZ, USA; Department of Dermatology, University of Lübeck (SK), Lübeck, Germany; INSERM UMR_S910, Aix-Marseille University (HE), Marseille, France; Memorial Sloan-Kettering Cancer Center (SD, AM), New York, NY, USA

Congenital melanocytic nevi (CMN) have historically been categorized according to lesion diameter. Krengel and colleagues (2013*) have proposed a new consensus based classification for CMN which includes projected adult size (PAS) and localization, number of satellite nevi, and morphological characteristics. The purpose of this study was to test the applicability of the new categorization scheme and to examine the relationship between the expanded classification system and the patient’s history of melanoma and neurocutaneous melanocytosis (NCM). Patients who have been diagnosed with CMN attended a patient care conference in 2012 and were offered the opportunity to participate. Anamnestical data were collected by a standardized questionnaire. Clinical examination was performed by two dermatologists, a nurse, and a nurse practitioner. In this sample (n=45), 33 patients had a giant CMN and were reclassified according to the new system. CMN size was positively correlated with NCM (p<0.05). The classification system allowed an easy and detailed phenotypical characterization of each individual CMN. CMN size and morphology were difficult to assess in patients after surgical removal and the number of satellite nevi at birth or in the first year of life was not always known. Meaningful conclusions regarding the correlation between CMN parameters and the risk of NCM and melanoma are limited by the small study sample. Our report provides practical aids for the application of the newly proposed CMN classification. Prospective evaluation of accurately classified patients in CMN registries will further reveal the predictive value of the scheme. * Krengel, S., Scope, A., Dusza, S.W., Vonthein, R., & Marghoob, A.A. (2013). New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. Journal of the American Academy of Dermatology, 68(3), 441-51. Doi: 10.1016/j.jaad.2012.05.043. Epub 2012 Sep 13.

Notes:
To date, 89 cases (from 17 countries) of congenital or congenital-type nevi of the nail unit have been prospectively included in the International register founded under the auspices of the International Dermoscopy Society launched in 2007. Inclusions are still ongoing. Recorded data are insufficient to give a complete figure of the natural history of these nevi however our preliminary findings are the following: 1. A large number of dermoscopically atypical lesions on early observations. 2. Many changes (enlargement) over time. 3. Frequent peri-ungual pigmentation. 4. When present, this periungual pigmentation often involves the distal part of the perionychium with a dermoscopical fibrillar pattern. 5. Plate erosions and triangular shape of the melanonychia striata longitudinalis are also common features. 6. Over time, lesions become dermoscopically more regular and several showed a marked tendency towards regression, some completely resolved over time. 7. No case of melanoma has been observed either at initial presentation or during follow-up. Since the five first features described above are very similar to what is observed in nail unit melanoma in adults, management of such cases is extremely difficult; however, the benign evolution observed in all cases for whom we have sufficient follow-up allows us to believe that observation should be preferred to systematic surgery in such cases. Inclusion of additional cases in the register (http://dermoscopy-ids.org/images/stories/nail_study.pdf) is encouraged. (Presented on behalf of the following co-authors: Alice PHAN, Brigitte BALME, Stéphane DALLE, Sébastien DEBABIEUX, Ralph P. BRAUN, Isabelle TROMME, Christelle NICOLAS, Olivia BORDALO, Elizabeth LAZARIDOU, Theresa CAO, Avi SHALOM, Agostino CRUPI, Bruno CAYATTE, Thomas BOLZINGER, Cristina CARRERA, Thomas Roger SCHOPF, Susana PUIG, Josep MALVEHY, Céline DAVaine, Anne Marie VIALLARD, Marta VALDIVIESO-RAMOS, Nicolas POULALHON, Nabil KABBARA, Philippe BAHADORAN, Ash MARGHOOB, David MORENO RAMIREZ, Carlo Alberto CAGALI, Osvaldo CORREIRA, Ana Margarida BARROS, Florence GRANEL BROCARD, Giuseppe ARGENZIANO, Giovanni PELLACANI, Michel D’INCAN, Rubina ALVEZ, Anna MARTINEZ DE SALINAS, Gabriella CAMPOS DO CARMO, Juliette MIQUEL, Masaru TANAKA, Christine CHIAVERINI, Christelle NICOLAS, Jean Pierre BERGUES, Radwan MAASARANI, Jeho MUN, Moonbum KIM, Robert BARAN.)

Notes:
Current practice in the treatment of congenital melanocytic naevi: a survey among clinicians in the Netherlands
Céline A.M. Eggen*, Joep G.J. Wijnand, Corstiaan C. Breugem, Chantal van der Horst, Wilma Bergman, Suzanne G.M.A. Pasmans
Dutch Society of Dermatology and Venereology (CE, see abstract), Utrecht, the Netherlands; Department of Pediatric Dermatology and Allergology, Wilhelmina Children’s Hospital, University Medical Center Utrecht (JW), Utrecht, the Netherlands; Department of Pediatric Plastic Surgery, Wilhelmina Children’s Hospital, University Medical Center Utrecht (CB), Utrecht, the Netherlands; Department of Pediatric Plastic Surgery; Amsterdam Medical Center (CH), Amsterdam, the Netherlands; Department of Dermatology, Leiden University Medical Center (WB), Leiden, the Netherlands; Department of Pediatric Dermatology and Allergology, Wilhelmina Children’s Hospital, University Medical Center Utrecht (SP), Utrecht, the Netherlands

OBJECTIVE: Opinions concerning prophylactic removal of congenital melanocytic naevi (CMN) vary among clinicians. This study was carried out to assess how clinicians in the Netherlands manage CMN of all sizes.

METHODS: A questionnaire was sent to all practicing dermatologists (470) and plastic surgeons (270) in the Netherlands. Questions on management were posed for children and adults in three size categories: large (LCMN, >20cm P.A.S.), medium (MCMN, 1.5-20cm P.A.S.) and small (SCMN <1.5cm P.A.S.). It was assumed there was no clinical suspicion of malignant melanoma. RESULTS: The survey was filled out by 165 dermatologists and 46 plastic surgeons (28.5%). At first encounter with a patient with LCMN, a wait-and-see policy was preferred by 60.5% (47/76) for children (CH) and by 70.3% (45/64) for adults (AD), instead of (referral for) treatment. If treatment was chosen, overall preferred treatment in LCMN was complete excision, with a few preferring curettage or laser ablation in children. Theoretically, 38.5% state they never prophylactically remove an LCMN, 34.1% always, and the remainder considers it up until a certain age. As for MCMN, main policy at first encounter is again wait-and-see (CH 75.8%, 122/161; AD 76.6%, 108/141), as it is for SCMN (CH 85.4%, 135/158; AD 83.8%, 129/154). In all size groups, the main factor in decision-making is a positive family history for melanoma. Other important factors are cosmetic issues, localisation, difficult morphology and wishes of the patient. Data analysis is still in progress. CONCLUSION: There is controversy regarding removal of CMN. In the Netherlands most prefer a wait-and-see approach, while a LCMN in a child is most likely to be treated (39.5%). We believe that the lack of consensus reflects to some extent the uncertainty in lifetime melanoma risk. (Submitted additionally on behalf of the other members of the Dutch Guideline Committee on ‘Congenital Melanocytic Naevi’: Albert Wolkerstorfer, Nicole Kuktsch, Simone Stadhouders, Marianne Crijns, Wolter Mooi, Hanneke Rijk-van Gent, Anja Ebus, Ferdie Keizers, Marjolein van Kessel.)

Notes:
Neurofibromatosis and large congenital melanocytic naevi
Pierre Moullot*, Dominique Casanova, Nathalie Degardin, Jacques Bardot
Assistance Publique Hôpitaux de Marseille (PM, DC, ND, JB), Marseille, France

Large congenital melanocytic naevi (LCMN) and neurofibromatosis type 1 (NF1) are distinct clinical entities. A diagnosis of neurofibromatosis is difficult to make in the presence of a congenital melanocytic naevus because nodules may arise in a naevus that have similar histopathological appearances to neurofibromata. Three cases with an association between those two entities are reported. All cases were first clinically diagnosed as LCMN: two were located on the face, and one on the scalp. Diagnosis of NF1 was worn by anatomopathologic and immunohistochemical analysis of associated skin lesions. Evolution of these cases and actions of reconstructive surgery performed since childhood are illustrated. The authors discuss the prevalence and etiologies of the association of those two pathologies. LCMN and NF1 are difficult conditions to take care of, especially when the two are combined. It is advisable to realize early diagnosis. It is important that histopathological findings are interpreted within a clinical context and S100 protein immunohistochemical stain is valuable in helping to differentiate these two conditions.

Notes:
Phacomatosis pigmentosa multiplex: long term follow-up in an adult patient
Géraldine Jeudy*, Daniel Lambert, Laurence Faivre-Olivier, Pierre Vabres
Department of Dermatology, University Hospital (GJ, DL, PV), Dijon, France; University Hospital, Department of Genetics and Center for Rare Diseases (LF), Dijon, France

Introduction: We report on the 20-year evolution of multiple giant congenital melanocytic nevi (CMN) superimposed on a large macular speckled lentiginous nevus (SLN). Case report: A 34-year-old man sought genetic counseling for an extensive congenital speckled lentiginous nevus on his lower trunk, perineum, buttocks and thighs with multiple superimposed large roundish hairy CMN. He was later examined at the age of 54. Comparison of photographs revealed that the SLN had acquired well-defined borders with darkening of its background macular component, and an increase in the number of darker spots. In contrast, the CMN had undergone partial regression. They were paler, covered with fewer hairs, wrinkled and had turned into chalazoderma. No malignant transformation had occurred.

Discussion: This combination of a large macular SLN with multiple large CMN has been suggested to be an example of twin spotting by Torrelo et al. who called it phacomatosis pigmentosa multiplex. Twin spotting is defined as the juxtaposition of two types of cutaneous nevi, sometimes involving different cell lineages. SLN can be associated with different cutaneous nevi such as a port-wine stain or an epidermal nevus, thus defining phakomatosis spilorosea and phakomatosis pigmentokeratotica, respectively. Post-zygotic HRAS mutations in phakomatosis pigmentokeratotica and NRAS mutations in giant CMN have recently been demonstrated. Here, we suggest that the SLN originated from an early post-zygotic mutation in neural crest cells and the superimposed melanocytic nevi arised from a second genetic event in the same cell lineage. It is noteworthy that the two melanocytic components underwent opposite evolutions: regression of the CMN contrasting with darkening of the SLN. Spontaneous regression of CMN has been reported in children but rarely in adults.

Notes:
Congenital melanocytic nevi with features of speckled lentiginous nevi
Sven Krengel*, Lisa Weibel, Hannah Hummel, Holger Haenssle
Department of Dermatology, University of Lübeck, Lübeck, Germany; Department of Pediatrics, Division of Pediatric Dermatology,
Children’s hospital Zürich, Zürich, Switzerland; Department of Child and Adolescent Health - Division of Neuropediatrics,
University of Goettingen, Goettingen, Germany; Department of Dermatology, University of Goettingen, Goettingen, Germany

Background: According to Schaffer et al. (2001), speckled lentiginous nevi (SLN; syn.: nevus spilus) are “inside the spectrum of congenital melanocytic nevi (CMN)”. Nonetheless, typical SLN and typical CMN are mostly regarded as distinct entities because of overt morphological differences. Overlap forms between those typical cases have been called “nevus spilus-like CMN” or “giant nevus spilus”. In some of these cases it is unclear whether they are morphological variants of conventional CMN or conventional SLN, or might represent a separate phenotype.

Material: The authors of this work collected four strikingly similar cases of giant CMN with a café au lait-like background macule. They differ significantly from conventional CMN, but also from large and giant forms of conventional SLN.

Conclusion: The phenotypical characteristics of these cases suggest a specific subtype of CMN. Criteria for the phenotype of “speckled-lentiginous-nevus-like congenital melanocytic nevi” (SLN-like CMN) are outlined. By these criteria, a differentiation of SLN-like CMN from a) inhomogenously pigmented conventional CMN (ipCMN) and from b) conventional (giant) SLN is possible in most cases. Moreover, SLN-like CMN have to be distinguished from the multiple medium CMN phenotype (mMCMN).
The giant nevus syndrome and phacomatosis pigmentokeratotica: the enlarging spectrum of mosaic pigment cell RASopathies
Nathalie Gosselin, Pierre Vergnes, Yves Perel, Fanny Morice-Picard, Khaled Ezzedine, Alain Taïeb*
Department of Dermatology and Pediatric Dermatology, National Reference Centre for Rare Skin Disorders, Bordeaux University Hospitals (NG, PV, YP, FMP, KE, AT), Bordeaux, France

The giant pigmented nevus (GPN) phenotype is usually more straightforward to diagnose than the much rarer phenotype of phacomatosis pigmentokeratotica (PKK), dominated by the epidermal nevus. We present a case of a girl born with a giant nevus covering 70% of the body surface with temporal epilepsy attributed to neurocutaneous melanosis (NCM), and well controlled under antiepileptic therapy. She had, in addition, hip dysplasia and a bilateral nephroblastoma treated with surgery and chemotherapy, with no current evidence of progression. Genetic testing for constitutional mutations of WT2 and P53 (indicated by cancers in family of the father) was negative. Interestingly, a linear epidermal lesion, not recognized on early dermatological evaluations, was found on the left arm, with some overlap with the melanocytic nevus. A similar observation with nephroblastomatosis in the context of PKK (Jacobelli et al., 2010) has been published, suggesting that the diagnosis in our patient was PKK. This observation suggests that we look for minor, non-melanocytic nevi in GPN. In addition, the recent molecular characterisation of NRAS (GPN-NCM) and HRAS (PKK) somatic mutations suggests convergence on common downstream molecular pathways which could explain other associated tumours such as nephroblastoma.

Notes:
CMN and the experience of itch: a snapshot of an ongoing patient based survey
Harper N. Price*, Judith O’Haver
Phoenix Children’s Hospital, Department of Dermatology (HNP,JO’H), Phoenix, AZ, USA

Background: It has been brought to our attention by our patients, the CMN community, and other colleagues, that pruritus in patients with large/giant CMN is a significant issue that impacts quality of life and may constitute an important medical problem. However, little information exists in the literature regarding the pruritus prevalence, and pathogenesis or treatments for this population. Only two single case reports in the literature demonstrate the psychological, physical and financial burden that itching in these patients can cause, due to the lack of treatments to control symptoms. It is our hope that understanding more basic information regarding the pruritus experienced by these patients will lead to further studies investigating the pathogenesis of pruritus in this cutaneous hamartoma and provide a baseline of understanding for potential treatment modalities. Methods: We developed a patient-based survey to gather basic information including prevalence, age of onset of itching, location of itching, severity of itching and treatments utilized. Due to the rarity of patients with large/giant CMN, we utilized a survey to collect data based on our survey questionnaire. The survey was developed using Survey Monkey, an online resource, which provided an online link to the survey and allowed us to post or email the link to make it more readily available. We aimed to have a minimum of 150 participants complete the survey. Basic descriptive statistics (median, mean, SD, percentages) will be completed on the available data by the existing Survey Monkey statistical tools. Results: Thus far, 132 subjects have completed the survey. The majority of subjects were female (60%) and age of participants ranged from less than one year of age to the 6th decade of life. The majority of participants were the legal guardian/parent of the person with the nevus (78%). Of 117 participants 59% experienced a problem with itch, in the past and/or currently. The most prominent area where itch was problematic was the back, and areas were often hypertrichotic or had overlying bumps. The most common treatment for itching was topical emollients and prescription topical corticosteroids. One-third of patients had their itchy areas of the nevus removed (n=22/65) Of these patients, 44% felt that their scar was still itchy and 33% felt the area was no longer bothersome. Summary/limitations: Itching remains a significant problem for patients with CMN. Because this is a patient based survey, this data was not verified by a physician and the majority of answers were given by the patient's caregiver. Quality of life and itch severity scores are currently being analyzed for all patients that have experienced itch in this survey.

Notes:
The pathology of congenital melanocytic nevi and neurocutaneous melanocytosis
Miguel Reyes-Múgica
Children’s Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, USA

This talk will present the histopathology of neurocutaneous melanocytosis in the central nervous system with previously undescribed findings, that of truly metastatic tumors in lung, liver, or bone marrow with no ventriculoperitoneal shunt dissemination, \textit{NRAS} mutational status, and further work in progress, including cell line characterization.

Notes:
Malignant melanoma occurring in patients with a large congenital melanocytic nevus: retrospective study of 10 cases
Sylvie Fraitag
Necker-Enfants Malades Hospital, Department of Pathology, Paris, France

Malignant melanoma (MM) is rare in children. The main risk factor is large congenital melanocytic nevus (LCMN) defined by a size in adulthood of at least 20 cm. The risk of melanoma on LCMN, is around 2%. We performed a retrospective study of 10 cases of melanomas in patients with a LCMN seen in our institution during a 27-year period. We collected clinical, morphological, immunohistochemical (HMB45, P16, MIB1) and fluorescence in situ hybridization (FISH) data. In our series, the average age of diagnosis of melanoma was 19 years with 2 distinct groups: 5 patients developed their melanoma before 5 years and 5 of them after 20 years. The mortality rate was 60% with an average age of death at 17.3 years. No clinical or histological prognostic factors were able to be identified. They were located within the CMN in 7 cases and outside the CMN, such as in the brain and lymph nodes, in 3 cases. They were mainly composed of large epithelioid cells. The CMN was located on the trunk in 8 cases and associated with satellite nevi in 6 cases. Their excisions were subtotal in 9 cases. Diagnosis was difficult only in 2 cases that developed MM during childhood and in these cases immunohistochemistry and FISH were not very helpful. Actually, FISH showed only numerical abnormalities in melanomas developed in childhood, whereas those developed in adulthood had both numerical and structural abnormalities in one case or numerical abnormalities in the other. MM occurring in association with LCMN have a heterogeneous presentation and prognosis. Histopathology remains the diagnostic gold standard but developments of new molecular tools such as CGH array could be promising.

Notes:
Case reports of melanoma in children and adolescents - a systematic analysis of the literature
Johanna Friesenhahn, Nina Gerdes, Johanna Neuhold, Sven Krengel*
Department of Dermatology, University of Lübeck (JF, NG, JN, SK), Lübeck, Germany

Background: Melanoma is a rare tumor in children (childhood melanoma, ChM). The literature indicates that 1) clinical and epidemiological characteristics of melanomas in this age group differ from adult melanomas and 2) distinct patterns can be discerned inside the group of ChM. Objective: To identify and analyse all detectable case reports and case series of ChM in the medical literature. Methods: A systematic medline search for ChM case reports was performed. A subdivision of ChM cases was undertaken into 1) ChM developing in absence of a CMN (ChMw/o CMN) and 2) ChM associated with a congenital melanocytic nevus (ChM+CMN). Results: 258 cases of ChMw/o CMN (206 cutaneous, 52 non-cutaneous) and 178 cases of ChM+CMN (114 cutaneous, 64 CNS) were identified. The mean age at diagnosis of fatal cutaneous ChMw/o CMN was 13.2 years. In ChM+CMN, mean age at diagnosis was 5.5 years (CNS melanoma, 5.8 years). The majority of CMN-associated cutaneous melanomas arose in small and giant CMN, compared to medium and large CMN. 53.9 percent of the CNS melanomas arose in patients with multiple medium CMN. Limitations: Case reports in the literature are inherently biased towards atypical and severe cases. Therefore, no epidemiological conclusions can be drawn from our data. Conclusions: Our analysis supports the concept that cutaneous ChM without CMN or associated with smaller CMN differ in several important aspects from ChM associated with large or giant CMN.

Notes:
Neurological abnormalities in children with congenital melanocytic naevi - a prospective 25 year study
Regula Waelchli
Great Ormond St Hospital for Children, London, UK

Children with congenital melanocytic naevi (CMN) seen in a tertiary referral department of a children's hospital from 1988-2013 were enrolled prospectively in a study of neurological MRI findings. The criteria for performing an MRI of the CNS were changed in 2008 subsequent to a published review of the results, to include only those with multiple CMN (i.e. two or more CMN) independent of site and size of lesions. This re-evaluation of the data from this large cohort compares the results from the last five years with the previous findings, and concludes that the 2008 guideline is appropriate in maximising the number of positive MRIs, without so far missing important neurological abnormalities. The categories of findings on MRI are described, and are compared with clinical neurological findings in the same population. Both outcome measures are associated with cutaneous and facial phenotypic classification, and with MC1R and NRAS genotype in a subset.

Notes:
Neurocutaneous melanocytosis associated with a large congenital melanocytic nevus: treatment and follow-up of one case
Guillaume Captier
CHRU Montpellier-UM1, Montpellier, France

Objectives: Neurocutaneous melanocytosis (NCM) with large congenital melanocytic nevus (LCMN) is a rare condition and is considered to have a poor prognosis. We report a case of NCM associated with LCMN. Material and methods: A female infant was born with a 20cm LCMN located on the back, associated with more than 20 satellite nevi. Surgical treatment for the LCMN started at 8 months, with tissue expanders and excision of some satellite nevi. At the same time, she developed daily complex partial seizures and impairment of consciousness with or without vegetative manifestations and tonic posture of the left arm. EEG video recordings confirmed the diagnosis of right temporal lobe epilepsy with pharmacoresistant evolution. Cerebral MRI showed a NCM in the right temporal lobe. After partial excision of LCMN with expanded flaps at 12 months, a temporal lobectomy associated with an amygdalo-hippocampectomy was performed at 14 months of age. Results: The histological results showed a non malignant NCM. The post operative period was simple. Because the patient remained seizure free, the antiepileptic drug was progressively stopped 1 year after neurosurgery. The post operative cerebral MRI at one year showed no lesions. We decided to pursue the excision of the LCMN. At 27 months, the LCMN was totally removed with expanded flaps. At 4.5 years, the patient remains seizure free with some psychomotor cognitive and language delays. Conclusion: In LCMN, the surgical strategy must be started early on, to reduce the maximum of the nevus and to have better results. When symptomatic NCM appears during the treatment of the LCMN, it raises the question of the continuation of the surgical strategy, taking into account the poor prognosis of the symptomatic NCM. In our case, the choice was to continue the surgical strategy to remove the LCMN after a latency period and good neurological evolution.

Notes:
Primary melanoma of the CNS in children is driven by congenital expression of oncogenic NRAS in melanocytes.
Canisius Wilhelmina Hospital (HKV), Nijmegen, the Netherlands; The Institute of Cancer Research (MP, AV, BSL), London, UK; Radboud University Nijmegen Medical Centre (PG, IvEG, JS, BK, PW, WB), Nijmegen, the Netherlands; Reinier De Graaf Hospital (JG), Delft, the Netherlands; Canisius Wilhelmina Hospital (WR), Nijmegen, the Netherlands; Cancer Research UK Centre for Cancer Therapeutics (IND, CS), Surrey, UK; The Paterson Institute for Cancer Research (RM), Manchester, UK

Activating mutations in NRAS, one of the three major isoforms of the RAS family of GTPase proteins, are common in human melanoma (15-20%). To produce a mouse model of NRAS-driven melanoma, we expressed oncogenic NRAS (NRASG12D) in mouse melanocytes. When NRASG12D was expressed in the melanocytes of developing embryos, it induced congenital melanocytic lesions of the skin but not cutaneous melanoma. However, it did induce congenital melanocytosis of the leptomeninges and early-onset primary melanoma of the central nervous system (CNS). The tumors were rapidly proliferating and caused neurological symptoms, rapid health deterioration and death. The disease observed in the mice resembled that observed in two cases of primary melanoma of the CNS in young children, both of which carried oncogenic mutations in NRASG61. Interestingly, one of these two children presented with a giant congenital melanocytic nevus (in the context of neurocutaneous melanosis) that shared the same NRAS mutation as his CNS melanoma (in the absence of any signs of primary skin melanoma). We conclude that acquisition of somatic mutations in NRAS in CNS melanocytes is a predisposing risk factor for primary melanoma of the CNS in children, and we present a mouse model of this disease. In addition, the observation of an identical NRAS mutation in the melanocytic neoplasms of both skin and CNS in one of the children could be explained by the hypothesis that early during embryogenesis one of the melanocyte precursor cells acquires a somatic NRAS mutation, which gives rise to a subpopulation of NRAS-mutated melanocyte precursors that further migrate to skin and leptomeninges, eventually resulting in congenital melanocytic neoplasms in these locations. This hypothesis is supported by a similar observation we made in an additional case of neurocutaneous melanosis presenting with CNS melanocytosis.

Notes:
Neurocutaneous melanocytosis: targets for treatment
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Background: Large congenital melanocytic nevi (LCMN) and associated neurocutaneous melanocytic lesions may harbor mutations in the NRAS pathway, as reported by others. We previously reported a patient with LCMN, NCM and seizures who underwent surgical resection for improved seizure control. The pathology was consistent with NCM without evidence of melanoma. Aim: We aimed to further elucidate the pathophysiology of NCM by confirming the presence of NRAS mutations, as previously described. Methods: DNA from the patient’s CNS tumor was isolated and subjected to an exon-capture-based next-generation sequencing platform as developed at MSKCC (IMPACT, Integrated Mutation Profiling for Actionable Cancer Targets). This assay screens for mutations in 275 cancer-associated genes. Results: We identified a somatic Q61K mutation in NRAS in 11% of reads from tumor DNA. No other mutations were identified in the remainder of genes sequenced. We propose that the NRAS pathway may be a target for future therapy.

Notes:
Surgical management of large and giant nevi: the role of tissue expansion in the “current state of the art”
Bruce Bauer
Division of Plastic and Reconstructive Surgery, NorthShore University HealthSystem, Northbrook, IL, USA

To date, the only method of excision of the all or the greater part of large and giant congenital melanocytic nevi (LCMN and GCMN) is excision of full thickness skin and underlying subcutaneous fat (excision to fascia). Reconstruction of the defects following this excision can only be accomplished with replacement of quality flap tissue. Given the extent of many of these lesions, tissue expansion is the only reliable method of accomplishing this reconstruction with optimal aesthetic and functional outcomes. Thirty years of experience with the largest surgical series of LCMN and GCMN has demonstrated that similar anatomic patterning of nevus involvement and long term follow-up has allowed for continued evolution of expansion techniques, and both helped minimize the number of surgical procedures required for a given pattern of nevus. Cases will be reviewed from all anatomic areas demonstrating how the procedures are sequenced and demonstrate both early and long term outcomes. The timing of procedures will be reviewed in regard to safety, and the benefit in regard to minimizing the psychosocial impact of these lesions will be emphasized.

Notes:
Skin expansion for congenital melanocytic nevi in children: our experience from 1990 to 2009
Anissa Belkhou*, Omar Abdel Wahab, Pierre Guerreschi, Véronique Duquennoy-Martinot
Service de Chirurgie Plastique, Reconstructrice et Esthétique, Hôpital Roger Salengro (AB, OAW, PG, VDM), Lille, France

Background: Skin expansion is a technique frequently used in plastic and reconstructive surgery for over two decades. In a pediatric population, the most common indications are for congenital melanocytic nevi, scars and alopecia. In our unit, we started to practice this technique in 1984 and congenital melanocytic nevi represent more than half of our indications. The aim of this study is to present our experience over twenty years. Patients and Methods: We included all the patients who had a skin expansion for melanocytic nevi and were under 15 years and 3 months old for the first operation, between 1990 and 2009. For each patient, we analyzed several data such as the number of protocols and prostheses, volume, type of reconstruction, results and complications. Results: Between 1990 and 2009, in our unit, 98 children had a skin expansion for congenital melanocytic nevi, with 131 surgical protocols and 195 prostheses. The most frequent indication was the scalp, in 58 cases. The average age at the first protocol was 40.4 months (3 years and 4 months); the youngest patient was 7 months old and had a lumbar skin expansion; the oldest one was 13 years and 10 months old and had a skin expansion of the arm. 76 children had only 1 protocol, and the average duration for a protocol was 94.1 days. 104 (53.3%) prostheses were crescent-shaped. 28 patients presented a complication: 5 during the post-operative period (2 requiring removal of the prostheses), 15 during the expansion (9 removals), and 8 complications during the reconstruction. We obtained a good initial result for 64 patients, but 32 children needed further intervention. Conclusion: Expansion is a good tool in pediatric surgery, especially for nevus removal, but precise planning is required in order to avoid problems, incidents and complications.

Notes:
Treatment of congenital pigmented nevi with tissue expansion based on our experience with 163 patients over ten years
Alexander Margulis
Hadassah Medical Center, Hebrew University School of Medicine, Jerusalem, Israel

Introduction: Surgical excision is the treatment of choice for congenital pigmented nevi. When confronted with lesions comprised of large surface areas that preclude primary approximation of margins, subcutaneous expansion of adjacent tissue and subsequent expanded reconstruction of the area excised is the method of choice. Methods: In this presentation, the authors provide an overview of the literature and present selected cases of their experience with tissue expansion in the pediatric population, covering different anatomical locations and their respective challenges. This experience is based on surgical treatment of 163 pediatric and adult patients with congenital nevi in a single center over a period of 10 years (2003-2013). Results: 119 pediatric patients (< 16 years) had 202 procedures of tissue expansion and 44 adult patients had 56 procedures of tissue expansion in the study period. The overall percentage of complications was 18.2%. There were 40 pediatric procedures with complications (19.8%) and 7 adult procedures (12.5%). The difference in complication rate between the two groups was not found to be statistically significant. There was no statistically significant difference in the complications rate between the different anatomical areas of expansion in both adults and pediatric patients or in the indications for operation. Most of the complicated cases eventually had a successful reconstruction (68%). Conclusion: If performed with careful attention to several key points, tissue expansion can provide a safe and effective method by which one can satisfactorily reconstruct exposed areas remaining after large nevi excision.

Notes:
Management of giant naevi of the face; review of 44 cases treated by full thickness skin graft, in one stage or after expansion
Isabelle James
Clinique du Val d’Ouest, Ecullly, France

Giant naevi of the face are among those most needing aesthetic surgery to improve the social and scholastic well-being of affected children. Beyond simple or expanded flaps, full-thickness skin grafts can be used for reconstruction. But this technique must imply rigorous choice of skin colour of the donor site so as to be the closest possible to the face. The authors reviewed 44 cases operated between 2 months and 10 years of age, where follow-up ranged between 1 year and 15 years. We conclude that surgeons should stop using abdominal or inguinal skin, because it tans differently over time and unwanted hair can grow at puberty, even if it seems to be simpler to perform a one-stage procedure for a large surface. The cervical region of an infant younger than 6 months, allows treatment of an area as large as the frontal headband in a one-stage operation. If a one-stage procedure is not possible using cervical skin, we prefer to use an expanded full-thickness skin graft. The tissue expander is inserted in the preclavicular region, and inflated in a way to develop a sufficient quantity of skin to treat all the surface of the naevus. The grafts must respect anatomical units so that the scars are hidden in the natural skin folds and in the hair lines, to avoid patchy aspects. Even using this procedure, physical therapy is necessary for at least one year after the operation, to obtain the closest colour and texture to surrounding tissues and smooth integration of the grafts; the parents must be informed of this point before the procedure.

Notes:
Face the challenge – The Zürich approach of reconstructive surgery for facial CMN
Clemens Schiestl
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Reconstructive surgery for CMN of the face is challenging, even for experienced surgeons. In addition, the risk of melanoma was initially overestimated and has now been adjusted to a lower percentage, which leads to an increased expectation towards an excellent aesthetic outcome after surgical treatment. Based on our psycho-social and ethical research, we are trying to adapt our approach with regard to the decision-making process including the child, the parents, and the multidisciplinary team. On the basis of selected patients, we want to illustrate our Zürich approach concerning the treatment of facial CMN. We will elaborate on the information that is given to the parents, on how to make a decision for or against surgery, and last but not least on our surgical strategies including different reconstructive options after excision of the CMN in the face. In an interactive part of the talk, some of our latest cases will be presented. Pictures of the patient before surgery will be shown and the first question will be asked of the audience and experts: “If it would be your patient, would you decide for surgery or not?” Then, the second question will be asked: “If surgery should be done, what would your plan be?” Following the discussion, we will present the further course of the child and discuss with the audience/experts if we - as a multidisciplinary team - made the right decision and how successful we were with each patient. The decision to opt for reconstructive surgery is - beside the reconstruction itself - a challenging issue, also for an experienced multidisciplinary team. An open-minded and interactive discussion may help us to reflect on our approach.

Notes:
Surgical arsenal in large congenital melanocytic nevi
Nathalie Degardin*, Jacques Bardot, Guy Magalon
Timone Enfants University Hospital Pediatric plastic surgery unit (ND, JB), Marseille, France; Conception University Hospital (GM), Marseille, France

Surgical treatment of the large melanocytic nevus is a real challenge for the plastic surgeon. Surgical removal engages the entire arsenal of plastic surgery, in order to reconstruct the skin defect caused by the surgery. Prior attention must be brought to the management of the capital of intact skin. The different times of surgery have to be well planned and explained to the family as soon as possible. Different criteria should be taken into account, such as age, location and axis of the nevus, potential complications and constraints of the surgery, psychology of the child and her family. The purpose of treatment is, first of all, resecting the area indicated by the dermatologist as suspicious, and to remove as much as feasible the lesions located in visible areas such as the face, limbs, upper trunk, and so forth. The reconstruction has to preserve function and maintain aesthetic appearance. All techniques of plastic surgery may be performed to achieve treatment of a giant nevus: curettage, serial excision, skin grafts (with or without dermal regeneration templates), skin flaps, tissue expansion or free tissue transfer after tissue expansion. Different cases will be presented and commented in order to illustrate the usable surgical arsenal, its typical results but also its limits and its complications.

Notes:
Psychological aspects of congenital melanocytic nevi
Ornella Masnari
University Children’s Hospital Zürich, Switzerland

The aim of this presentation is to give an overview of research findings concerning psychological aspects of having a CMN and to discuss their implications for the multidisciplinary management of patients with a CMN. The main question will be: how can individuals with CMN – and their families – be best supported? In recent years, there has been an increasing interest in psychological aspects of having a visible difference. However, so far, there are only a few published studies focusing on individuals with CMN. Findings suggest that a CMN puts a child at higher risk of experiencing emotional difficulties; however, there is a large inter-individual variance and many affected children do not demonstrate any difficulties. Research among children and adolescents with various facial differences (e.g., birthmarks or burn scars) has demonstrated that a facial difference negatively affects the way a child is perceived and treated by others. Individuals with a visible difference often experience social stigmatization, including being stared at, pity, avoidance, or bullying. Notably, perceived stigmatization has been shown to be an important predictor of psychological adjustment and health-related quality of life. This fits well with other research findings which suggest that psychosocial factors (e.g., quality of family environment, social skills, or coping strategies) are more predictive of individual adjustment than are physical features (e.g., size or location) of a condition. A comprehensive support of individuals with CMN should, therefore, be provided by a multidisciplinary team and include not only biomedical but also psychological counseling. The latter should be provided through both routine care (e.g., assisting parents/patients in the decision making process regarding treatment) and specialist interventions (e.g., coping strategies workshops). Moreover, public health interventions are needed to raise awareness of CMN and to reduce stigmatization of people with CMN.

Notes:
The intense study of melanoma and other cancers due to misregulation of the MAPK signaling pathway, and the development of the concepts of germline and somatic RASopathies, have been beneficial to understanding some of the basic biology of prenatal nevus formation. Conditional gains of function in various components of this pathway have been generated in a number of vertebrate models. I will discuss the pros and cons of today’s zebrafish, chick and mouse models, including new ones currently being developed in our and other laboratories, and their contributions to better understanding human pathology.

Notes:
What about a mouse model for the congenital giant naevus?
Lionel Larue
CNRS UMR3347, INSERM U1021, Institut Curie, Orsay, France

Notes:
Characterization of initiating cells in large congenital melanocytic nevus
Romain Fontaine, Christelle Charbel, Natacha Kadlub, Aurore Coulomb-L’Hermine, Arnaud Picard, Selim Aractingi, Sarah Guégan*
CdR Saint-Antoine, Inserm UMRS 938, UPMC (RF, CC, SA, SG), Paris, France; Hôpital Necker, Department of Maxillofacial and Plastic Surgery (NK), Paris, France; Hôpital Trousseau, Department of Pathology (ACL), Paris, France; Hôpital Necker, Department of Maxillofacial and Plastic Surgery (AP), Paris, France

Large congenital melanocytic nevus (ICMN) is a benign tumor present at birth resulting from a proliferation of melanocytes in the dermis and/or epidermis, with a clear risk of melanoma transformation. Ontogeny of this peculiar self-limited proliferation remains poorly understood. Here, we addressed the question of whether some cells act as initiating stem cells in ICMN. In vivo, ICMN express melanocytic lineage markers MelanA and MITF; malignant melanocytic stem markers ABCB5 and stem cell/progenitors lineage markers Sox10, Nestin and Oct4. In vitro, roughly one ICMN initiating cell out of 250 cells formed sphere colonies that could be passaged. ICMN specimens were xenografted in Rag2−/− mice and expanded macroscopically (473% growth) after 7 months. Within the outgrowth skin tissue, we found BrdU+ melanocytes that displayed the same benign nested architecture than in the original nevus. Cell suspensions from ICMN were also mixed with immortalized keratinocytes and xenografted in Rag2−/− mice. Both types of cells proliferated and reconstituted the architecture of the human epidermis with its characteristic melanocyte layout, lentiginous hyperplasia and nested architecture. These data show that certain subtypes of congenital nevi cells display features of initiating cells, supporting the hypothesis of a stem cell as the origin of this tumour.
Restoring original donor skin colour by addition of melanocytes to skin substitutes
Sophie Böttcher*, Thomas Biedermann, Agnes Klar, Clemens Schiestl, Martin Meuli, Ernst Reichmann
University Children’s Hospital Zürich, (SB, TB, AK, CS, MM, ER), Zürich, Switzerland

Background: Autologous skin substitutes are being used more and more to cover large skin defects. So far, they do not systematically contain melanocytes, although these are essential for solar protection and skin pigmentation. In this study we reconstructed dermo-epidermal skin substitutes containing melanocytes and studied them in an animal model. Donor skins of different pigmentation types were used and features pertinent to skin colour were analyzed. The skin substitutes were then compared to the original donor skin from which it was derived. Methods: Keratinocytes, melanocytes, and fibroblasts were isolated, cultured, and expanded from skin biopsies of light and dark pigmented patients. For each donor, melanocytes and keratinocytes were seeded in different ratios (1:1, 1:5, 1:10) onto collagen gels previously populated with autologous fibroblasts. Skin substitutes were transplanted onto full-thickness wounds of immuno-incompetent rats, were observed during 8 weeks, then macroscopic and microscopic analyses were conducted with regard to skin colour (chromameter evaluation), and structural epidermal features. Results: Chromameter evaluation revealed that skin colour of reconstructed light and dark pigmented skin was very similar to donor skin, independent of which melanocyte/keratinocyte ratio was added. Also, the skin colour remained constant throughout the transplantation time. Microscopically, epidermis formation and stratification, as well as melanocyte and melanin distribution within the epidermis were also almost identical to the donor skin. The melanocyte seeding ratio did not produce any measurable difference. Conclusion: These data suggest that the patients’ native skin colour can be sustainably restored by adding autologous melanocytes to bioengineered dermo-epidermal skin substitutes and remains constant after transplantation in an animal model.

Notes:
Tethered Kit-ligand/c-kit mediated niche-anchorage and signaling is kinase independent and imatinib insensitive
Séverine Tabone-Eglinger, Zuleika Calderin-Sollet, David Boettiger, Bernhard Wehrle-Haller*
University of Geneva (STE, ZCS, BWH), Geneva, Switzerland; University of Pennsylvania, Philadelphia, USA

The tyrosine kinase receptor c-kit, and its ligand, Stem Cell factor or Kit-ligand (KitL), are critical for the development and maintenance of melanocytes, germ cells, mastocytes and hematopoietic stem cells. Alternative splicing of KitL generates two transmembrane proteins, which form membrane-bound (mb) or generate soluble (s) KitL. In order to study the interaction of c-kit expressing cells with their respective environmental niche, and to understand the mechanisms of niche signaling, we analyzed c-kit expressing melanoblasts, mast cells (MC/9), as well as c-kit mutant expressing fibroblasts for their ability to respond to tethered KitL. We show the formation of stable, mb-KitL/c-kit containing clusters at sites of MC/9 contacts with fibroblasts, providing resistance to physiological shear stress. The clusters recruited tyrosine-phosphorylated proteins and induced spatially restricted F-actin polymerization. Mutational analysis demonstrated kinase-independent mb-KitL/c-kit clustering, anchorage, F-actin polymerization and Tyr567-dependent cluster phosphorylation. Kinase inhibition by imatinib blocked cluster coalescence and spreading by soluble KitL, but allowed cluster phosphorylation, F-actin polymerization and spreading on immobilized KitL/fibronectin, requiring PI3K recruitment and juxtamembrane residues. From these results, we propose a new, “mechanically-induced”, drug-resistant function of c-kit, which provides signaling and anchorage to the environmental niche, explaining drug resistance and dormancy of various stem cell populations.

Notes:
Role of mast cells in scar formation

Arul Veerappan, Barbara Summers, Jacqueline Brazin, Alicia Potuck, Chih-Chang Chu, Randi Silver*  
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Introduction: Inflammation is central to the wound healing process and inflammatory cells are prominent in traumatized tissue. Mast cells (MC), found in the skin and in increased numbers in nevi, are part of the inflammatory response. However, their role in wound healing has not been well defined. MC renin-angiotensin (ANG II) and histamine are fibrogenic. We hypothesize that MC play a critical role in wound healing and if over-stimulated, trigger extracellular matrix dysfunction and abnormal wound healing in Giant Congenital Melanocytic Nevi (GCMN).

Methods: MC-deficient WBB6F1-Kitw/Kitw mice (MCD) and their congenic controls WBB6F1-+/+(CC) (JAX #100410) underwent incisional wound surgery on the dorsal side and the wound sutured closed. Mice were sacrificed 3, 7 and 14 days post-surgery. The incisional wound area/scar was excised and processed for light microscopy. Gomori trichrome staining was used to qualitatively assess collagen deposition. Freshly isolated human and mouse dermal fibroblasts (FB), maintained in short term culture, were screened for histamine and ANG II receptor expression and their fibroproliferative potential. Results: The incisional wounds were healed by day 14 in the CC and MCD mice. In the CC mice a progressive increase in skin thickness (normal <7d <14d) was discernable at the wound site consistent with more abundant collagen deposition. In the MCD mice, the thickness of the scar tissue and the collagen abundance were noticeably less. Isolated dermal FB were found to express the histamine H1 (56 kDa) and ANG II AT1 (43 kDa) receptor subtypes. Exposure of FB to histamine and ANG II led to proliferation. Conclusion: Our results demonstrate that MC and their mediators contribute to scar formation. Their increased numbers in nevi may lead to abnormal wound healing in GCMN patients.

Notes:
Mast cells are increased in skin of patients with giant congenital melanocytic nevi
Cláudia Salgado, Randi Silver, Bruce Bauer, Dipanjan Basu, Lori Schmitt, Abdelhadi Rebbaa, Yasmin Khakoo, Miguel Reyes-Múgica*
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Background: Mastocytes (MC) and nevocytes (NC) derive from different progenitors but share regulation by stem-cell factor (SCF), a cytokine fundamental for differentiation and proliferation of MC and for spatial distribution and activation of NC. Both MC and NC express the SCF receptor, CD117 (KIT). We hypothesize that MC hyperplasia is associated with NC proliferations of Giant Congenital Melanocytic Nevi (GCMN). Aim: To investigate MC number and distribution in GCMN compared to normal skin. Methods: Tissues from 24 GCMN, 4 uninvolved skin samples from GCMN patients and 5 normal skin samples. MC were detected and analyzed on 5 µm paraffin sections stained with Giemsa, and MC-tryptase immunohistochemistry; CD117+ cells were also assessed. Slides were scanned using the Aperio Scanscope at 20X and counted using Image J software (NIH). The relative abundance of MC-tryptase in GCMN and control samples was analyzed by Western blot (WB). Statistical analysis was performed by ANOVA and Tukey tests. Results: A higher MC density in nevus tissue compared with control skin was observed with Giemsa staining. Further analysis revealed increased numbers of tryptase+ MC in GCMN tissues (78 ± 31.1 MCs/mm²) compared with skin from individuals without GCMN (30.3 ± 9.9 MC/mm²); p=0.002. Numbers of MC in tissues from patients with GCMN were not different in the nevus compared with uninvolved skin (60.22 ± 22.8 MC/mm²) p=0.286; similar results were seen by WB analysis, showing comparable tryptase amounts. CD 117 expression was strong in MC, but nevocytes were also CD117-positive with increasing intensity in more superficial nevus cell layers. Conclusions: Our results indicate that the skin of patients with GCMN has a higher density of MC than control skin. This may explain the abnormal wound healing and allergic reactions described in GCMN patients.

Notes:
RASopathies: the spectrum of constitutional disorders of RAS/MAPK activation
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RASopathies designate collectively a series of disorders due to (usually) activating mutations that dysregulate the RAS/MAP (mitogen-activated protein) kinase transduction pathway. RASopathies are clinically heterogeneous, but a subgroup of 4 clinically related disorders form the majority of the family, namely Noonan syndrome (NS – major genes: \textit{PTPN11} and \textit{SOST}), NS with multiple lentigines (NS-ML), cardiofaciocutaneous syndrome (CFC- major gene: \textit{BRAF}) and Costello syndrome (CS – unique gene: \textit{HRAS}) and their clinical variants. Neurofibromatosis type 1 (NF1), Legius syndrome, metachondromatosis and vascular-capillary malformation syndrome also belong to the RASopathy family of disorders, but will not be discussed as they have clearly different clinical manifestations. RASopathies are a common (1/2000), clinically and genetically heterogeneous group of dominantly inherited conditions characterized by distinctive facial features, and, frequently, short stature, chest deformity, congenital heart disease (CHD), cardiomyopathy (CMP), learning disabilities or cognitive impairment and other comorbidities including a mild susceptibility to hematologic and other malignancies. Penetrance of RASopathies is probably close to 100%, but expressivity is quite variable, and many patients who do not express the classic features remain undiagnosed. Dermatological manifestations of RASopathies are variable. Some are common to all clinical varieties, and others are more tightly linked to one gene. Dry skin is common. Palmar and plantar hyperkeratoses are more common in CFC and CS. Hair is often curly. Scalp hypotrichosis mainly concerns CFC, whereas ulerythema ophryogenes is common in NS and CFC. Sexual pilosity is sparse or absent. Loose skin characterizes CS. Diffuse hyperpigmentation is observed with mutations of \textit{HRAS, SHOC2} or \textit{RIT1}, whereas patchy pigmentary lesions are observed in Legius and NF1. Naevi are common in all forms, but they are profuse (lentiginosis) with some specific mutations of \textit{PTPN11} and \textit{RAF1}. Benign skin tumors are common in NF1, but also in CS (periorificial papillomas). Surprisingly, none of the RASopathies has been associated with an increased risk of melanoma.

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   p 24*: Surgical management of large and giant nevi: the role of tissue expansion in the “current state of the art”.
   p 37: Mast cells are increased in skin of patients with giant congenital melanocytic nevi.

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   p 5*: Collisions of Interest.

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p 34: Restoring original donor skin colour by addition of melanocytes to skin substitutes.

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p 22: Primary melanoma of the CNS in children is driven by congenital expression of oncogenic NRAS in melanocytes.


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p 35: Tethered Kit-ligand/c-kit mediated niche-anchorage and signaling is kinase independent and imatinib insensitive.

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p 36: Role of mast cells in scar formation.

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p 21*: Neurocutaneous Melanocytosis associated with a Large Congenital Melanocytic Nevus: Treatment and follow-up of one case.

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  p 31*: Animal models for CMN, NCM and related conditions: pros and cons.
  p 9: Application of revised criteria for classification of congenital melanocytic nevi in a selected population.

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  p 15: The giant nevus syndrome and phacomatosis pigmentokeratotica: the enlarging spectrum of mosaic pigment cell RASopathies.

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p 18*: Malignant melanoma occurring in patients with a large congenital melanocytic nevus: retrospective study of 10 cases.

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p 19: Case reports of melanoma in children and adolescents - a systematic analysis of the literature.

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p 14: Congenital melanocytic nevi with features of speckled lentiginous nevi.

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**p 27**: Management of giant naevi of the face ; review of 44 cases treated by full thickness skin graft, in one stage or after expansion.

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**p 13**: Phacomatosis pigmentosa multiplex : long term follow-up in an adult patient.

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**p 33**: Characterization of initiating cells in large congenital melanocytic nevus.

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**p 23**: Neurocutaneous melanocytosis: targets for treatment.  
**p 37**: Mast cells are increased in skin of patients with giant congenital melanocytic nevi.

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**p 6**: The genetics of congenital melanocytic naevus syndrome.

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**p 34**: Restoring original donor skin colour by addition of melanocytes to skin substitutes.

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**p 14**: Congenital melanocytic nevi with features of speckled lentiginous nevi.  
**p 19**: Case reports of melanoma in children and adolescents - a systematic analysis of the literature.  
**p 9**: Application of revised criteria for classification of congenital melanocytic nevi in a selected population.

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**p 13**: Phacomatosis pigmentosa multiplex : long term follow-up in an adult patient.

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**p 32**: What about a mouse model for the congenital giant naevus?

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p 8*: The congenital melanocytic nevus registry in Catalonia: results of a multidisciplinary network of centers.

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p 22: Primary melanoma of the CNS in children is driven by congenital expression of oncogenic NRAS in melanocytes.

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p 7*: The challenge of managing congenital nevi: remove or not remove?
p 9: Application of revised criteria for classification of congenital melanocytic nevi in a selected population.

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p 26*: Treatment of congenital pigmented nevi with tissue expansion based on our experience with 163 patients over ten years.

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p 30*: Psychological aspects of congenital melanocytic nevi.

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p 17*: The pathology of congenital melanocytic nevi and neurocutaneous melanocytosis.
p 37*: Mast cells are increased in skin of patients with giant congenital melanocytic nevi.

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p 28*: Face the challenge – The Zürich approach of reconstructive surgery for facial CMN.
p 34: Restoring original donor skin colour by addition of melanocytes to skin substitutes.

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p 10*: Congenital nevi of the nail unit : The International Dermoscopy Society register experience.

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p 22: Primary melanoma of the CNS in children is driven by congenital expression of oncogenic NRAS in melanocytes.

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p 35*: Tethered Kit-ligand/c-kit mediated niche-anchorage and signaling is kinase independent and imatinib insensitive.

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p 14: Congenital melanocytic nevi with features of speckled lentiginous nevi.

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We have the privilege to welcome to Marseille the exceptional prize-winning photographer, Rick Guidotti, director of Positive Exposure. Founded in 1998, Positive Exposure is a non-profit organization that challenges the stigma associated with difference by pioneering a new vision of the attractiveness of diversity. Positive Exposure uses photography and video to transform public perceptions of people living with genetic, physical and behavioral differences. Mr. Guidotti will open a public exhibit, during the weekend of the CMN Expert Meeting, of photographs featuring the beauty of people affected with large congenital melanocytic nevi. He will also propose on-site photo shoots of patient advocate volunteers attending the conference.

Before the opening on Friday, 27 September, 2013, Mr. Guidotti will conduct a public lecture in English about Positive Exposure. This is hosted by the Department of Medical Genetics and Functional Genomics, INSERM UMR_S910, in Amphitheatre 7 (5th floor, red wing) of the Faculté de Médecine, University Aix-Marseille from 11:30a.m.-12:30 p.m. Contact us for more details.

Mr. Guidotti has given numerous talks about his work and goals and is also a regular speaker for public outreach events such as the annual American Society for Human Genetics' high school workshop and a recent fundraiser for childhood genetic disorders by the HudsonAlpha Institute for Biotechnology. Positive Exposure’s educational and advocacy programs reach around the globe to promote a more inclusive, compassionate world where differences are celebrated.

Find out more about Positive Exposure at www.positiveexposure.org.

Announcement of the availability of this conference’s recordings will arrive shortly in your mailboxes.

Proceeds to Naevus Global.