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Dr Michelle MURROW

Clinical and Genetic Studies on Cutis Laxa: The Pittsburgh Experience

Cutis laxa is a rare disease, which challenges affected individuals, family members, medical professionals and researchers. To address these challenges, our team has successfully maintained and expanded a research study on cutis laxa since 2002 with funding from the National Institutes of Health and other organizations. Our study has enrolled 176 families and 365 individuals to date. At the University of Pittsburgh we established a bi-annual research clinic to study how cutis laxa affects the body's major systems, and to improve its diagnosis using new technologies: skin elasticity measurement and 3-dimensional facial imaging.

Out team investigates the genetics of cutis laxa using the latest DNA sequencing and microarray technologies. As part of our research, we search for disease-causing changes in 14 genes related to cutis laxa, and we scan the entire genome to identify new genes. We study the consequences of the genetic changes on cellular metabolism, cell secretory pathways, elastic fiber formation and growth factor signaling using skin cells grown from samples donated by patients, cells genetically modified to resemble cutis laxa cells, and zebrafish models. Our studies have uncovered unexpected connections between elastic fibers and growth factor signaling. These new discoveries increase our knowledge about how genetic changes interact with cellular functions and provide a foundation for designing new molecular therapies for cutis laxa.

Our research has resulted in 27 publications and over 70 conference presentations on cutis laxa to date. To share information and increase awareness, we maintain a web site: cutislaxa.pitt.edu.

Dr Bert CALLEWAERT, MD, PhD

European patient registries: a tool to understand the diversity in Cutis Laxa syndromes

The term 'cutis laxa syndrome' comprises different clinical conditions that are characterized by a loose, redundant skin and variable involvement of other organ systems including the skeleton, central nervous system, eyes, lungs and heart and vessels.

Delineating the different entities both at the clinical and molecular level is important for multiple reasons:

1. To improve the diagnostic process
2. To guide patient management and follow-up

3. To provide accurate family counseling
4. To facilitate communication between and among patients, clinicians and researchers
5. To increase patient awareness of their condition and as such open perspectives for patient-empowered research and patient-centered clinics
6. To find anchor points for therapy
7. To delineate novel entities

In this presentation we will illustrate the necessity for larger European or global collaboration, both through registries and clinical care by the identification of two novel cutis laxa entities in our recent research experience. We will position these objectives within the framework of the European Reference Networks that are currently being established for rare disorders and provide examples of ongoing patient empowered initiatives in a related disorder, arterial tortuosity syndrome.

Dr Romain DEBRET

Development of an elastin substitute: first tests with Williams-Beuren and cutis laxa cells *in vitro*

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Elastin-like peptides (ELP) are excellent examples of biomimetic polymers recently proposed in regenerative medicine, particularly for soft tissue engineering (skin, blood vessels, lung ...) for which modeling is a complex task requiring functional elasticity to instruct cells properly. Fine-tuning of ELP's primary structure can modulate or improve physicochemical, structural and functional properties of the native protein. In addition, the adjustment of ELP physicochemical characteristics through external stimuli (temperature, pH) defined them as intelligent polymers. These bioactive polymers thus provide a wide range of very promising applications in tissue engineering and drug delivery, although this has been under-explored until then.

We have developed and characterized a synthetic elastic protein called Elactiv'. This elastin substitute is inspired by the unique structure of the human tropoelastin, the soluble precursor of elastin. Elactiv' retains main physicochemical characteristics (thermo-responsive behavior, self-assembly properties) and biological functions (proliferation, differentiation and survival of human dermal fibroblasts, susceptibility to enzymatic degradation) of the native protein. Besides, Elactiv' is able to incorporate into neo-synthesized elastic fibers by healthy dermal fibroblasts. Another remarkable feature of Elactiv' is the ability to re-induce the synthesis of fibrillar tropoelastin deposits by fibroblasts isolated from Williams-Beuren syndrome patients. Ongoing analyzes in the laboratory are designed to observe whether this phenomenon can also occur using elastin-mutated cells isolated from cutis laxa patients.

Dr Maxime ETIENNE, Prof Ludovic MARTIN

Pseudoxanthoma elasticum and Cutis Laxa: diseases with similarities and differences!

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Introduction

Pseudoxanthoma elasticum (PXE) is an inherited connective tissue disorder that has similarities with Cutis Laxa (CL), particularly in the skin. However, extra-cutaneous PXE manifestations are usually less severe than in CL. After a general explanation of PXE we discuss the similarities and differences between PXE and CL, focusing on the therapeutic aspects of PXE.

What is Pseudoxanthoma elasticum ?

PXE is an inherited autosomal recessive connective tissue disorder (1-3), i.e. a patient requires an abnormal copy of both the mother's and the father's disease gene to develop PXE. PXE is characterized by fragmentation and progressive aberrant calcification of elastic fibres. Elastic fibres provide flexibility in the connective tissue, for example they allow the skin to regain its original state when stretched. PXE is caused by a loss of function of the ABCC6 gene (4). The prevalence of PXE is estimated to be 1/25 000 in Europe. PXE mainly affects the skin, retina and large arterial blood vessels (1-3.5). Cutaneous manifestations occur mostly during childhood or adolescence (6), developing initially in the form of yellowish papules, sometimes confluent plaques, mainly on the sides of the neck and flexural areas (in particular antecubital, axillae and popliteal fossa). These lesions are asymptomatic but may be considered disfiguring by the patient. Ocular manifestations are firstly asymptomatic. The ophthalmological features of PXE initially present "peau d'orange" on fundoscopy. Then tears develop ("angioid streaks") and sometimes neovascularisation with the risk of retinal hemorrhage and scarring that can lead to permanent blindness. Cardiovascular manifestations are also initially asymptomatic, with a decrease in peripheral arterial pulse rate. In more severe cardiovascular manifestations there is intermittent claudication on walking (pain in the legs on walking or running, requiring the patient to stop the activity) (5). There also seems to be an increased risk of cerebral stroke (data submitted for publication). Cardiac and coronary events are very rare (7). Although, there are elastic fibres in the lungs, patients with PXE have no respiratory symptoms.

The evolution of cutaneous, ocular and cardiovascular manifestations is unpredictable and independent. Skin manifestations are usually the first clinical focal indications that suggest the diagnosis of PXE (6). The diagnosis of PXE is based on a combination of suggestive skin lesions, compatible microscopic abnormalities on skin biopsy and the retinal damage described above (8.9). However, the absence of skin lesions does not exclude the diagnosis of PXE and, in rare atypical forms or without skin lesions, identification of a mutation of the ABCC6 gene is necessary (1,10).

Similarities between Pseudoxanthoma elasticum and Cutis Laxa

CL and PXE are connective tissue disorders. As described above, PXE is characterized by fragmentation and aberrant calcifications of elastic fibres. CLs are a group of disorders characterized by a wrinkled appearance, with redundant, inelastic skin caused by lack of synthesis of elastin, another structural protein of elastic fibres, or an enzyme of the extracellular matrix (11). Thus, in most forms of CL, elastic fibres are also affected, but there is no calcification of the elastic fibres in CL.

Clinically, forms of CL represent a group of disorders characterized by a redundant and pleated aspect of the skin and loss of skin elasticity (12). These skin manifestations are also seen in the forms of PXE with highly developed skin lesions, especially in forms known as "PXE-like disease" associated with mutations of the GGCX gene (13). In PXE-like disease, skin manifestations are very extensive and PXE is one of the differential diagnoses of CL.

Differences between Pseudoxanthoma elasticum and Cutis Laxa

Although there are similarities between PXE and CL, there are also many differences. First, in PXE elastic fibres are initially normal then deteriorate, becoming "dystrophic". On the other hand, in CL production of elastic fibres is abnormal. The elastic fibres are "dysplastic". Moreover, PXE is essentially a single inherited autosomal recessive disorder (although there are very rare inherited forms unrelated to the ABCC6 gene, and forms that are acquired, not inherited). CL corresponds to a group of diseases that are mostly inherited or, more rarely, the consequence of another pathological condition or of a treatment (14). Among the inherited forms, some are autosomal recessive CL (e.g. with mutations of FBLN4, FBLN5, LTBP4, ATP6V0A2, PYCR1, P5CS, GORAB, RIN2 genes). Others are autosomal dominant CL (the patient receiving the disease gene from one parent or being the first familial case, e.g.CL with mutations of ELN and FBLN5 genes). For CL with mutation of the ATP7A gene, transmission is recessive X-linked (more complex form of inherited disease; boys developing the disease by transmission of the disease gene on the maternal X chromosome) (12).

Skin manifestations, which in PXE are mainly located on the neck and flexural areas, in CL can affect the entire body surface area. Extra-cutaneous CL manifestations are very different and depend on a mutated gene. According to the mutation, extra-cutaneous and in particular vascular, neurological and lung manifestations can be fatal. This is the exception for PXE patients (12,14).

In terms of treatment, recent progress in understanding the pathophysiology of PXE has opened up new perspectives for future treatment (15-18). In coming years PXE patients could expect disease progression to stop or regression of clinical manifestations of PXE. However, the treatment is currently exclusively symptomatic. Skin manifestations require surgical correction of skin surplus. When there are cardiovascular manifestations, it is necessary to eliminate cardiovascular risk factors, including smoking. Finally, ocular manifestations require regular monitoring by an ophthalmologist as soon as retinal features of PXE occur in order to initiate ranibizumab injections (19).

Recent identification of genes involved in different forms of CL and improved understanding of the pathophysiology of CL carry the hope of innovative treatment. Gene therapy is a promising therapeutic approach in this area. For example, a combination involving copper supplementation and gene therapy appears promising in occipital horn syndrome experiments in mice (20).

Conclusion

PXE and CL have some similarities but there are more differences that make them distinct diseases. PXE and other connective tissue disorders such as Ehlers-Danlos syndrome are raised in the differential diagnosis of CL. The possibilities of future treatments for CL will require greater understanding of the pathophysiology of the disease.

Most of the progress is based on the existence of multidisciplinary clinical and pre-clinical teams, fully involved with patient organizations, and collaborating international networks to obtain adequate research funding.

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