



7th International Conference on Ectodermal Dysplasia (ED) 1st International Course on ED

April 12-14, 2018
Murcia, Spain

ABSTRACT BOOK

Thursday, 12 April 2018

Opening lecture

Ectodermal dysplasias (ED): overview and international classification system review.

Pr. John T. Wright. Director of Strategic Initiatives. School of Dentistry. University of North Carolina, USA.

An international advisory group met at the National Institute of Health in Bethesda (Maryland, USA) to advance ongoing work towards establishing a classification system that would allow integration of both clinical and molecular information in a logical and systematic manner. Based on previous classification systems and current approaches to diagnose ectodermal dysplasias, a working definition for inclusion was proposed. Ectodermal dysplasias are genetic conditions affecting the development and/or homeostasis of two or more ectodermal derivatives, including; hair, teeth, nails, and glands. Genetic alterations known to be associated with ectodermal dysplasias but that affect only one tissue will be grouped as non-syndromic traits of the causative gene. (e.g. non-syndromic hypodontia or missing teeth associated with EDA gene mutation). Information for categorization and cataloging would include the phenotypic features, Online Medelian Inheritance in Man number, mode of inheritance, molecular defect, pathway involved. Major pathways elucidated to involved ectodermal dysplasias include EDA, WNT-Related, and P63 related pathways.

Session 1: Dermatological aspects in ED

Update in Sweat gland dysfunction

Pr. Smail Hadj Rabia. Department of Dermatology, Reference center for genodermatoses and rare skin diseases (MAGEC), INSERM U1163, Université Paris Descartes-Sorbonne Paris Cité, Institut Imagine, Hôpital Universitaire Necker-Enfants Malades, Paris, France.

Sweat is mostly produced by eccrine sweat glands and contains soluble electrolytes, metabolites and proteins. Sweat secretion acts primarily as a key thermoregulatory mechanism dissipating body heat. It plays also an important role in

promoting skin moisturizing and beneficial microflora growth and in fighting skin infections. Eccrine gland dysfunctions are associated with different genetic disorders that might be classified into three major groups: 1) diseases related to abnormal or defective gland innervation (for example insensitivity to pain); 2) diseases related to abnormal or absent eccrine sweat gland (ex: X-linked hypohidrotic ectodermal dysplasia), and more recently 3) diseases related to abnormal sweat composition with normal sweat glands. For example, the Ca²⁺ release from the endoplasmic reticulum is important for normal sweat production. This release is abrogated in patients presenting with isolated anhidrosis and normal sweat glands, and carrying *ITPR2* gene mutations.

Dermatological Care in ED

Dr. Ana M. Victoria-Martínez, MS, Teresa Martínez-Menchón, MD, PhD & Paloma Sánchez-Pedreño, MD, PhD. Dermatology Service. Hospital Clínico Universitario Virgen de la Arrixaca. IMIB-Arrixaca. University of Murcia. Spain.

Ectodermal dysplasia (ED) syndromes are a diverse group of rare inherited disorders, that affect multiple structures of ectodermal origin (skin, hair, teeth, nails, sweat glands, mucous glands and sebaceous glands).

To prevent the development of the symptoms in early childhood, promising therapeutic approaches are currently under clinical investigation. In this context, timely diagnosis of this genetic syndrome is crucial. Besides the time-consuming genetic analysis, clinical diagnosis can be made in patients with the full syndrome, but it can be difficult in partial cases and in carriers of the disease. In such cases, it is necessary to perform additional tests to demonstrate decreased sweating or a decreased number of eccrine glands such as the Minor test or skin biopsy. In the last years, some non-invasive imaging methods, such as optical coherence tomography and the reflectance confocal microscopy have been developed and are able to measure sweat glands and to detect sweat gland dysplasia.

The most frequent abnormality in ED is skin disorders, followed by hair and nail disorders. Recently, patients with hypohidrotic/anhidrotic ectodermal dysplasia (H/AED) have been reported to have a higher prevalence of symptoms suggestive of atopic disorders than the general population. It is unclear, however, what causes the impaired skin barrier function in H/AED patients but it is thought that reduced sweat production might be related. From a clinical point of view, the eczematous characteristics of HED skin resemble those of atopic dermatitis (AD), except periorbital dermatitis and periocular hyperpigmentation, that could be more characteristics of H/AED skin lesions, therefore treatment regimens are often similar to AD. Hair findings include abnormal structure, quality, quantity and patterns of distribution. Progressive hair loss may lead to total alopecia, usually by puberty. No special pharmaceutical agent is available to improve hair growth but some treatments have been reported with a favorable outcome.

Complete care of an ED patient is so complex that many different aspects of care must be managed together by a group of specialists, including dermatologist. It is important to provide a proper skin care, and that emphasizes the benefit of dermatologic involvement, and the need for increased awareness of the cutaneous disease in ectodermal dysplasias.

Honor Lecture

Orofacial manifestations in ED and principles for dental treatment

Pr. Birgitta Bergendal. National Oral Disability Centre for Rare Disorders. The Institute for Postgraduate Dental Education, Jönköping, Sweden.

Oral symptoms are prominent both in hypohidrotic ED, and in many other ED diagnoses. They include delayed tooth eruption, tooth agenesis, small tooth size, aberrant tooth form, mineralization disturbances, and low salivary secretion rates. Symptoms often include difficulties to swallow, chew and speak. Many children, from families both with and without a known history of ED, are diagnosed by a dentist when the first primary teeth do not appear as expected. The challenge for the dental team is to recognize children with ED among those with isolated tooth agenesis, which is seen in 6-10 % of the population. Oligodontia, defined as the congenital absence of six or more permanent teeth, third molars excluded, is found in around one in a thousand children, while ED is far less prevalent. If the diagnosis of ED was set at birth, or even during pregnancy, it would be beneficial for the family as they could be informed and prepared to cope with the symptoms. Even if dental aspects of ED have been reported in many publications, most of the information is anecdotal and dominated by single case reports, while evidence of best clinical practice is scarce. As in the field of rare disorders in general other methods for development of good clinical practices can be used, i.e. consensus conferences, care programs established by specialists in dentistry and medicine in cooperation with patient support groups, quality registries, and other research strategies based on collective experience. Patients with ED often have frequent dental contacts during the years they grow up, from infancy to adulthood, for treatment and for monitoring of oral health. This requires all care to be based on a fundament of trust, and performed without pain, and that the family, and later on the child, is informed and involved in decisions about treatment.

Session 2: Dental and Eye Management in ED

How can we treat the dental absences in ED?

Dr. Ekaitz Valle Rodriguez. Maxillofacial Surgery Service. Hospital Clínico Universitario Virgen de la Arrixaca. Murcia, Spain.

Ectodermal dysplasia is an uncommon genetic syndrome that affects at least two tissues from the ectoderm. It has been described 154 possible combinations. Hypohidrotic ectodermal dysplasia (Chist Siemens Touraine syndrome) is the most frequent type. Its transmission is especially X-linked form. The second one is Hidrotic ectodermal dysplasia or Clouston syndrome with an autosomal dominant form transmission. Hypohidrotic ectodermal dysplasia (HED) is characterized by hypotrichosis (sparseness of scalp and body hair), hypohidrosis (reduced ability to sweat), and hypodontia (congenital absence of teeth) with a characteristic facial aspect. Hypodontia or anodontia is associated with atrophy of alveolar bone process. This is an important problem for children affected by this syndrome due to functional difficulty (chewing, swallowing...) and dental aesthetic that must be corrected, depends on the age and teeth existing, in order to avoid psychologic and socialization problems. The management of these cases can be through prosthetic treatment: mucodental supported or mucoimplant supported prosthesis, orthodontic treatment, surgical treatment: dental implants, bone grafts or orthognathic surgery, as well as new treatments with stem cells therapy.

Clinical experience in osseus craniomaxillofacial reconstruction in ED

Dr. Ignacio García Recuero. Oral and Maxillofacial Surgery Department. Craniofacial Surgery Unit. Hospital Universitario Doce de Octubre. Madrid, Spain.

Ectodermal dysplasias is a group of conditions in which there is abnormal development of the skin, hair, nails, teeth or sweat glands. There are many different types of ectodermal dysplasias and each type of dysplasia is caused by specific mutations in certain genes.

In addition to its other symptoms, ectodermal dysplasia causes anodontia and hypodontia intraorally. Prosthodontic rehabilitation can be accomplished with fixed, overdenture, complete or implant-retained prostheses. Age is crucial factor for rehabilitation also the number and condition of present teeth. The replacement of teeth by implants is usually restricted to patients with completed craniofacial growth. The severe hypodontia or anodontia related with ectodermal dysplasias patients reveals insufficient the conventional prosthodontic rehabilitations. Dental implants are a valuable tool to achieve a fixed rehabilitation improving the functional and aesthetic condition of these group of growing patients. In patients with severe anatomic deficiencies autologous bone grafting is mandatory prior to place dental implants. The possibility of correct the malocclusion by orthognatic bimaxillary surgery combined with autologous bone grafting is the gold standard in craniofacial reconstruction for ectodermal dysplasias patients.

Eye management in ED: Ophthalmological manifestations in Hypohydrotic Ectodermal Dysplasia

Pr. M^a Dolores Romero Caballero. Ophthalmology Service. Hospital Universitario Reina Sofía. University of Murcia, Spain.

Ectodermal dysplasias form a group of diseases that result from the abnormal formation of tissues derived from the embryonic ectoderm, affecting: skin, teeth, hair, nails, sweat glands and sebaceous glands. In the skin, the dysfunction of the sweat glands limits the ability to regulate body temperature with sweat -hypohidrosis-. The main ophthalmological manifestations are periorbital pigmentation and hypotrichosis of eyebrows and eyelashes, but the most severe clinical consequence is due to evaporative dry eye produced by agenesis or dysgenesis of Meibomian glands (sebaceous glands of the eyelids).

Meibomian glands usually produce lipids that provide stability to the eyes tear film, and avoid its evaporation. In ectodermal dysplasias, the absence of eyebrows and eyelashes and alterations in the conjunctival and corneal epithelium destabilize even more, the tear film, triggering the inflammatory process in the ocular surface.

Early treatment with artificial tears is necessary asymptomatic patients. It is essential to inform about the chronicity of symptoms and the importance of controlling environmental factors (humidifying environments, avoiding drafts, rationalizing the use of computer screens and consoles in children, ...).

Session 3: Original ED Clinical Cases

Pr. Gianluca Tadini, Dermatology Service. Ospedale Universitario L. Sacco. Coordinator of the Center for Inherited Cutaneous Diseases. University of Milan. Italy

Unraveling the galaxy of rare syndromes with ectodermal anomalies, we discuss some case of great interest for both clinicians and geneticists, starting from Oculo-Dento-Digital syndrome and Schopf-Schultz-Passarge syndrome, crossing Ectodermal-dysplasia-skin fragility syndrome to conclude approaching three even rarest syndromes as Allgrove syndrome, X-Linked Pigmentary disorder with systemic manifestations and CIPA syndrome.

All this disorders will be extensively explained phenotypically and genotypically.

Friday, 13 April 2018

Session 4: Genetics in ED

National program for molecular characterization of ED Spanish patients: importance of multidisciplinary clinic and genetic counselling (P114/01259; P117/00796)

Pr. Encarna Guillén Navarro, Medical Genetics Section, Pediatrics Department. Hospital Clínico Universitario Virgen de la Arrixaca. IMIB-Arrixaca. University of Murcia (UMU). CIBERER-ISCIII, Murcia, Spain.

Dr. M^a Carmen Martínez Romero, Biochemistry and Clinical Genetics Center. Hospital Clínico Universitario Virgen de la Arrixaca. IMIB-Arrixaca. CIBERER-ISCIII. UCAM, Murcia, Spain.

Ectodermal Dysplasia (ED) diagnosis is usually established through the clinical phenotype and most cases are detected in pediatric or dermatology departments. In Spain, to date, confirmatory genetic tests have been very limited due to the lack of available technologies in public health services. From our hospital a multicenter program has been launched for the early diagnosis of ED in which patients are evaluated by a multidisciplinary care team (dentists, maxillofacials, dermatologists and geneticists) allowing a complete clinical and genetic characterization as well as a comprehensive follow-up and accurate genetic counselling. 92 ED patients and 115 first-degree relatives were included, most of them affected by Hypohidrotic Ectodermal Dysplasia (HED). The initial project focused on a complete analysis of 4 genes (EDA, EDAR, EDARADD, WNT10A). Subsequently, other types of ED were included, many of them with overlapping features which address the importance of implementing new genetic techniques to screen more genes at the same time. We have designed a new protocol including a NGS (Next Generation Sequencing) panel of 96 ED genes and Array-CGH+SNP 180K to increase the molecular genetic efficiency and it is available for all ED patients. The integral approach of this ED Spanish program is an example of best practice and a promising step to ED personalized medicine.

The genetic characterization has been carried out thanks to donations from AADE (*Asociación Española de Afectados por Displasia Ectodérmica*). The complete diagnostic strategy, as well as the investigation of new genes involved in the different types of ED and functional studies are supported by Instituto de Salud Carlos III (ISCIII), Spain Ministry of Economy and competitiveness, grant numbers: P114/01259 and P117/00796 and co-financed by FEDER (Fondo Europeo de Desarrollo Regional).

Genotype-phenotype correlation in Hypohidrotic ED

Pr. Holm Schneider, Head of the Center for Ectodermal Dysplasias & the Division of Molecular Pediatrics, University Hospital Erlangen, Germany.

Not yet available

Session 5: Non invasive Prenatal Diagnosis (NIPD) in ED

NIPD by DNA analysis in maternal blood

Dr. Ana Bustamente Aragonés, Genetics Service. Fundación Jiménez Díaz-Hospital, Madrid, Spain.

The presence of circulating cell-free fetal DNA (ccffDNA) in maternal blood allows non-invasive prenatal diagnosis (NIPD) of fetal genetic disorders. NIPD has been implemented in many prenatal diagnosis units for the study of different fetal conditions. However, NIPD of monogenic disorders is currently limited to some diseases and only available in a few laboratories.

Because of the coexistence of maternal and fetal DNA in the maternal plasma sample, NIPD has been initially limited to the study of paternally inherited or *de novo* alleles that are not present in the maternal genome. Based on presence/absence criteria of Y-chromosome specific sequences, fetal sex determination for pregnancies at-risk of X-linked diseases (like X-Linked Hypohidrotic ectodermal dysplasia, XLHED) has been one of the first studies to be offered. Although this approach did not allow knowing the fetal status for the disease, incorporation of this test has reduced conventional prenatal diagnosis in approximately 50% of these pregnancies.

Regarding autosomal disorders, analysis of the paternal mutation can be used to achieve a fetal diagnosis of a dominant disorder with paternal origin or to readjust the fetal risk in case of recessive diseases. Hence, NIPD of some monogenic disorders such as Cystic Fibrosis or skeletal dysplasias have been translated to clinical practice by the analysis of a panel of frequent mutations. Additionally, bespoke tests can also be developed for those families with other different mutations.

As for the non-invasive diagnosis of maternally inherited disorders, the coexistence of maternal and fetal DNA in the sample makes this diagnosis more challenging. However, the application of more sensitive technologies like next generation sequencing (NGS) and digital PCR (dPCR) is opening the NIPD field to the analysis of maternally inherited fetal disorders.

NIPD of Hypohidrotic ED by Tooth Germ Sonography

Dr. Johanna Hammersen, German Competence Centre for Children with Ectodermal Dysplasias, Department of Pediatrics, University of Erlangen-Nürnberg, Erlangen, Germany.

Objective: X-linked hypohidrotic ectodermal dysplasia (XLHED), a developmental disorder characterized by malformation of hair, teeth, and sweat glands, results from defective ectodysplasin A1 (EDA1) caused by EDA mutations. Inability to sweat, the major problem of XLHED which can lead to life-threatening hyperthermia, has been shown to be amenable to intrauterine therapy with recombinant EDA1. The aim of this retrospective study was to evaluate the diagnostic accuracy of tooth germ sonography as a non-invasive means to identify affected fetuses in pregnant women with EDA mutations.

Methods: Tooth germ sonography was performed in 38 cases at 10 study sites between gestational weeks 18 and 28. XLHED was diagnosed if fewer than six tooth germs were detected in mandible and/or maxilla. In all subjects, diagnoses were verified postnatally by EDA sequencing and/or clinical findings (standardized clinical assessments of hair, sweating, and dentition; panoramic dental radiographs). Estimated weights of 12 affected male fetuses and postnatal weight gain of 12 boys with XLHED were assessed using appropriate growth charts.

Results: In 19 of 38 sonographic examinations of 23 male and 13 female fetuses, a prenatal diagnosis of XLHED was made. The diagnosis proved to be correct in 37 cases; one affected male fetus was missed. Specificity and positive predictive value were both 100%. Tooth counting by clinical assessment corresponded well with radiographic findings. We observed no weight deficits of subjects with XLHED in utero but occasionally during infancy.

Conclusions: Tooth germ sonography is highly specific and reliable in establishing a prenatal diagnosis of XLHED.

Session 6: Social and ethical aspects in ED

Genetic data protection and use

Pr. Magnolia Pardo-López, Constitutional Law Department. University of Murcia. Chair in Bioethics and Health Law (University of Haifa, Israel). Director of Spanish Unit UMU-UNESCO. Murcia, Spain.

Not yet available

Informed Consents in ED Clinical Trials

Pr. Angus Clarke, Medical Genetics Cancer & Genetics, School of Medicine, Cardiff University, Wales, UK.

Recruitment to clinical trials of novel treatments for rare diseases raises challenges for the conduct of trials, as does the making of decisions by parents about consent for children to participate. A recent trial assessed the safety and efficacy of a novel protein-based treatment for X-linked hypohidrotic ectodermal dysplasia (XHED). The experiences and views of both professionals and the parents of participating infants were sought in telephone interviews that explored the parents' decisions made on behalf of their affected children.

The strong motivation of many parents to permit their infants to participate was striking, even when their participation entailed major disruption of family life. This was often grounded in a sense of obligation to the child and to living affected relatives, as well as a wish to contribute to knowledge and the future.

The trial demonstrated a lack of toxicity from the treatment but equally a lack of efficacy. There are good grounds for anticipating that treatment early in the third trimester of pregnancy would be effective. The next step is therefore a trial of treatment to be given in utero.

Our collective lack of familiarity with this context - of therapeutic trials for rare genetic disorders in which parents have to make proxy decisions about the potential participation of their children in the trial - makes it more difficult to know when the factors motivating an individual to participation may be "excessive" - whether they are of external origin or self-imposed.

Are there potential pressures that may be especially relevant in this context of clinical trials of neonatal or fetal treatment for rare genetic disorders? Are there lessons that we should draw from this case, which may be important in the protection of participants in other disease contexts?

Rare diseases and Social Security benefits: protection needs and legal responses

Pr. Belén García-Romero, Labour Law and Social Security University of Murcia. Chair in Bioethics and Health Law (University of Haifa, Israel). Executive Committee Spanish Unit UMU-UNESCO. Murcia, Spain.

Not yet available

Session 7: Update in X-linked Hypohidrotic ED (XLHED) diagnosis and treatment research

Automatic recognition of the XLHED phenotype from facial images.

Pr. Smail Hadj Rabia. Department of Dermatology, Reference center for genodermatoses and rare skin diseases (MAGEC), INSERM U1163, Université Paris Descartes-Sorbonne Paris Cité, Institut Imagine, Hôpital Universitaire Necker-Enfants Malades, Paris, France.

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a genetic disorder that affects ectodermal structures and presents with a characteristic facial appearance. The ability of automated facial recognition technology to detect the phenotype from images was assessed. In Phase 1 of this study we examined if the age of male patients affected the technology's recognition. In Phase 2 we investigated how well the technology discriminated affected males cases from female carriers and from individuals with other ectodermal dysplasia syndromes. The system detected XLHED to be the most likely diagnosis in all genetically confirmed affected male patients of all ages, and in 55% of heterozygous females. Interestingly, patients with other ED syndromes were also detected by the XLHED-targeted analysis, consistent with shared developmental features. Thus the automated facial recognition system represents a promising non-invasive technology to screen patients at all ages for a possible diagnosis of ectodermal dysplasia, with greatest sensitivity and specificity for males affected with XLHED.

Pharmacological stimulation of EDAR signaling and prenatal therapy of XLHED – update on ER004.

Pr. Holm Schneider, Head of the Center for Ectodermal Dysplasias & the Division of Molecular Pediatrics, University Hospital Erlangen, Germany.

During embryonic development, tissues and organs form in spatiotemporally defined successions of events until the organism has acquired its final shape. These events can be irreversibly affected if specific signals are not provided at the appropriate time. The morphogen Ectodysplasin A (EDA) participates in the development of skin appendages and other ectodermal derivatives. In X-linked hypohidrotic ectodermal dysplasia (XLHED), EDA deficiency irreversibly impairs sweat gland formation. Inability to sweat, which precludes normal thermoregulation, can lead to cot death and throughout life to hyperthermia-related illness.

When recombinant Fc-EDA (a fusion protein made up of the constant domain of the immunoglobulin G1 and the receptor-binding portion of EDA) or an antibody that activates the EDA receptor (EDAR) were administered repeatedly into the circulation of pregnant EDA-deficient mice, the disease phenotype of the pups was corrected, yet dams (homozygous for the loss-of-function mutation) did not benefit from treatment. The same was true when Fc-EDA was delivered directly into the amniotic fluid

surrounding EDA-deficient fetuses. Our recent experimental findings support a critical role of the neonatal Fc receptor in drug uptake from amniotic fluid. This receptor mediates uptake of IgG from mother's milk across the gut endothelium of rodents. Toxicity studies in monkeys showed that Fc-EDA was well tolerated. In three human patients with XLHED, intra-amniotic administration of Fc-EDA at gestational weeks 26 and 31, or at week 26 only, restored sustained sweating ability. All treated subjects had normal sweat duct densities at the soles of the feet, while their untreated older brothers lacked sweat ducts there and could not sweat at all. The treated infants had not developed XLHED-related morbidity by 14-22 months of age.

Combined with the ability to identify affected individuals by non-invasive sonographic prenatal screening, pharmacologic stimulation of EDAR signalling *in utero* represents a promising new approach to correct XLHED.

EspeRare relaunches XLHED's only treatment, ER004 (aka EDI200), as an antenatal therapy for boys with XLHED.

Agnes Jaulent, Translational Project Leader, EspeRare. Switzerland.

EspeRare is a unique not-for-profit drug developer based in Geneva, that specialises in accelerating the development of medicines for children suffering from rare diseases. Following Prof Holm Schneider's promising results from the in-utero interventions on XLHED foetuses, EspeRare was approached in 2017 by Edimer to see if they could relaunch the programme with this new challenging administration approach.

EspeRare's unique business model will be presented, as well as an outline of EspeRare's clinical plans for the antenatal administration of XLHED.

Session 8: Patient Advocacy Groups and European Reference network

EURORDIS

Mr. Denis Costello

Spanish Eurordis Office, Spain.

In early 2017, the European Commission approved the first European Reference Networks (ERN). ERN are networks for clinicians and researchers to share expertise, knowledge and resources across the EU. ERN will facilitate the sharing of knowledge, experience, medical research, teaching, training and resources. They use relevant communication and eHealth tools to enable the mobility of expertise across borders, rather than the movement of patients that travel to access care and expertise that does not exist in their country. EURORDIS, the European Rare Disease Organisation plays an important role in ensuring the participation of patient representatives in the establishment of ERN through various activities which Denis Costello will describe during this session of the 7th International Conference Ectodermal Dysplasia.

FEDER

Mr. Juan Carrión

President FEDER, Spain.

Not yet available

EDIN

Mr. Jose Manuel Montoya

Spanish Representative EDIN

The Ectodermal Dysplasia International Network (EDIN) is a non-profit organization established in 2007 by the Ectodermal Dysplasia National Leaders from around the world. It is the umbrella organization which facilitates greater collaboration and co-operation to benefit those affected by Ectodermal Dysplasia. Members advocate at national and international level to raise awareness amongst Scientific, Clinical and Lawmaker Communities.

AADE

Mrs. Gema Chicano

President AADE, Spain.

The patient association is playing an increasingly important role, and that is why it was very necessary to found and fight for our association. National Association on Ectodermal Dysplasia (AADE), in Spain, while short of important financial means, boast a very strong commitment amongst its members.

During the nearly 14 years since it was established, AADE attained a total membership of 60 families,; over 100-130 people with ED.

AADE has collaborated closely with others International Associations from the very beginning AADE has adviser to a significant number of people with ED, in Spain and Ibero-America; human right, disabilities, healthcare, basic needs, etc.

Currently, Social Security System, in Spain, includes dental implants and grafts, an important achievement for people with ED and theirs dignity.

At this time, the question is how we can strengthen and deepen this Association in the coming years

Oral communications

Thermoregulation in Hypohidrotic Ectodermal Dysplasia (HED)

Dr Heather Massey, Dr James House, Prof Michael Tipton.

Extreme Environments Laboratory, Department of Sport Science Science, University of Portsmouth, UK.

Hypohidrotic Ectodermal Dysplasia (HED) is a rare genetic disorder for which a substantial literature exists regarding the genetic variations and overt physical disorders such as sparse hair, oral and maxillofacial and dermatological conditions, and lack of sweat gland function. Comparatively less is known about thermoregulation in HED; other than high infant mortality, that may occur as a consequence of hyperthermia or fever (Clark, 1987). Skin blood flow may also be affected (Brenngleman, 1981), limiting heat loss. The limited knowledge of thermoregulation has led some medical practitioners to suggest reducing physical activity for patients with HED. This study assessed heat loss in children and adolescents with either a genetic or clinical diagnosis of HED who performed intermittent treadmill exercise and recovery in 30 °C air (60 % relative humidity). 15 patients were assessed and the presentation will present information from this group whilst focusing on two case studies which express the variability in thermoregulation in HED.

Skin blood flow was elevated when deep body temperatures increased, skin blood flow was also maintained during cooling interventions; providing a pathway for enhanced heat loss. Consequently, heat loss interventions which can cool the skin can be used to reduce excess stored heat. The case studies indicate the variability of sweat production with case A being able to sweat sufficiently to regulate his deep body temperature, whereas case B sweated little and his deep body temperature rose rapidly during exercise, but was able to cool using a cooling intervention.

Due to variability in the responses, thermoregulation in HED should be assessed on a case-by-case basis and potentially monitored before and after puberty for signs of sweating. Although many children or adolescents with HED may have little means to regulate deep body temperature through sweating, pragmatic cooling interventions can enable participation in physical activity.

Full mouth rehabilitation in patients affected by Ectodermal Dysplasia: orthodontics, orthognathic surgery and implant-prosthetic treatment. A 15 years route

Dr. Evangelista Giovanni Mancini; F.Gallo, F. Grecchi, F.Zingari, R. Bianco, R. Bianco, P.Gulinatti. Department of Maxillo–Facial Surgery, IRCCS Galeazzi Hospital. Milan, Italy.

Ectodermal Dysplasia (ED) is a sindromic condition that leads to disability for the oral cavity and for the facial structures. It is characterized by endetulous conditions which can determine maxillary atrophy in various degrees of seriousness. The number and the position of teeth can influence both the jaw bone development (influenced by the alveolar process) and the function of the stomathognathic apparatus.

In growing patients the above mentioned issues are functional (chewing and phonation) and psychological. Furthermore, in oligo and anodontia cases there are other issues that present themselves with respect to the following: vertical dimension, controlling the progression of maxillary atrophy and establishing partial or total removable prosthesis.

The ED Italian project and the clinical experiences has developed in the last 15 years and it has concentrated in curing all types of atrophy and endetulous conditions related to ED using and, often combining the following therapies: reconstructive or

orthodontic procedures, implants and orthognathic surgery. The correct clinical diagnosis is discussed and reviewed by all the members of the ED team (orthodontists, gnathologists, implantologists, and maxillo-facial surgeons). The therapies given to our patients are based on tests shared amongst the ED team. The therapies vary from orthodontic therapy to implants, in cases where patients have been diagnosed with mild or moderate oligodontia, and to the use of regenerative techniques and implantology therapy (including zygomatic therapy). These cures can be combined with orthognathic surgery in cases where the patient suffers from dysmorphia and severe atrophy.

The heterogeneity of the pathological histories and the diverse expectations of each patient point to the need for an individually specific treatment.

Dental treatment in young patients with EEC Syndrome (video projection)

Pr. Antonio L.Gracco. Department of Neurosciences. Section of Dentistry, University of Padua, Italy.

Most of the patients with EEC Syndrome have a severe clinical condition of Hypodontia.

Hypodontia is a frequent feature of the ectodermal dysplasias and dental problems are a common concern in this group of patients.

Unfortunately permanent oral rehabilitations are possible only in adult patients when the skeletal maturation is completed.

Temporary oral rehabilitations as removable partial dentures are often uncomfortable for young patients even if they can provide a good compromise both for aesthetic and function.

In these last years for young patients with tooth agenesis we are using a new operative protocol that combines crowns with skeletal anchorage provided by miniscrews. These screws can be inserted into the bone and can be removed in any time, even after some years. This procedure can reduce patient discomfort and can guarantee a natural appearance of the smile.

Face and hands surgery in EEC Syndrome's patients (video projection)

Prof. Franco Bassetto.

EEC International Observatory. Plastic and Hand Surgery Clinic. Department of Neurosciences, University of Padua, Italy.

In the video, Prof Bassetto presents the steps guidelines for surgical interventions, related to the face and the limbs. Guidelines created with the p63 EEC Syndrome International association.

Scientific research on EEC Syndrome corneal's aspects (video projection)

Prof. Vincenzo Di Iorio. Molecular Medicine Department, Padua University, Italy.

In the video, Prof. Di Iorio talks about the current research study on corneal staminal cells in patients with different types of EEC syndrome.

POSTER COMMUNICATIONS

Experiences of Living with Oligodontia and Undergoing Oral Habilitation

Solfrid Sørgerd Saltnes^{1,2}, Hilde Nordgarden² Rønnaug Sæves², Janicke Liaaen Jensen¹ Amy Østertun Geirdal³.

1 Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, 2 TAKO-centre, Lovisenberg Diaconal Hospital, 3 Oslo University College of Applied Sciences.

Background: Individuals with oligodontia may experience psychological complaints because of unacceptable aesthetics and reduced orofacial function. They have reported significantly higher levels of anxiety and lower quality of life (QoL) in comparison with individuals with some other craniofacial conditions and a normative population.

Aims: To evaluate the individuals' experiences of living with oligodontia and undergoing oral habilitation.

Methods: Twelve participants (6 females and 6 males, aged 21-48) were included in this qualitative study. Eight participants had clinically diagnosed ectodermal dysplasia and four had isolated oligodontia. All received a formal written invitation and consented to participate in a semi-structured interview using an interview guide. The questions in the interview guide were based on results from previous research and clinical experience. All interviews were digitally recorded and transcribed. The transcripts were coded and analyzed manually using a phenomenological method of analysis. The Regional Ethics Committee approved the study.

Results: The participants described experiences associated with themes like; a feeling of being different, psychological challenges, the burden of treatment, the importance of shared decision-making, the impact of rehabilitation on self-esteem, and the use of coping strategies. Several reasons for experiencing psychological challenges were described, but lack of teeth and the long time waiting for, and undergoing, dental treatment were highlighted. Completing oral habilitation and positive attitudes among health care personnel regarding shared decision making were stressed as very important factors, positively influencing the experiences of psychological distress, QoL, and well-being.

Conclusion: A more holistic, coordinated, and multi-professional treatment approach in the treatment of oligodontia seems to be the ultimate goal.

Family with lacrimo-auriculo-dento-digital syndrome: clinical description and molecular characterization

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Lacrimoauriculodentodigital syndrome (LADD syndrome OMIM#149730) is a multiple congenital anomaly syndrome characterized by hypoplasia, aplasia or atresia of the lacrimal system; anomalies of the ears and hearing loss; hypoplasia, aplasia or atresia of the salivary glands; dental anomalies and digital malformations. These patients can also present with renal anomalies, cleft lip and/or palate and hypospadias. Autosomal dominant inheritance with variable expressivity, with pathogenic mutations described in FGF10, FGFR2, FGFR3 and TP63 genes.

We present a family with two affected members with LADD syndrome associated to FGFR2 gene.

Index case: 3 year-old-boy born with cleft lip and palate and dysplastic ears; short stature. Family data: Mother: 32 years old, healthy. Short stature: 144.5 cm (-3.28 DE). Father: 39 years old, short stature: 149.5 cm ($p < 1$, -4.37 DE). Alacrimia, dental anomalies (small teeth, poor tooth enamel), hepatic steatosis, chronic laryngitis, nursemaid's elbow, auricular dysplasia, and second-third syndactyly in hands and feet. 5 year old sister with short stature ($p < 1$, -4.76 DE), small teeth and auricular dysplasia. Medical history: Normal pregnancy, detection of cleft lip in US at 21 week gestation. Born at term, normal delivery. Birth weight 2820 g ($p < 27$), Length: 45 cm ($p < 1$, -2.42 DE), OFC: 34 cm ($p < 16$). Tearing during first months of life. Physical exam (3 years of age): Weight: 9,6 kg, $p < 1$; -2.76 DE, Length: 85 cm, $p < 1$; -3.9 DE; OFC: 47.9 cm; $p < 2$, -2.06 DE. Wide forehead, hypertelorism, dry eyes, right cleft lip, hypoplastic right nare, right cleft palate, dysplastic ears, small teeth and low thumbs.

Cardiac evaluation, spine X-ray and CGH-array with normal results. Clinical exome sequencing identified a not previously described variant c.1875_1902del in FGFR2 gene, a frameshift deletion which produces a premature stop codon and segregates with the phenotype in the family.

We present a new mutation, expanding the molecular spectrum of FGFR2 in a LADD syndrome family with variable expressivity (study supported by Instituto de Salud Carlos III (ISCIII), Spain Ministry of Economy and competitiveness, grant numbers: PI14/01259 and PI17/00796 and co-financed by FEDER (Fondo Europeo de Desarrollo Regional)).

Clinical description of two cases of Trichothiodystrophy 4 due to homozygous mutation in MPLKIP in two unrelated families from the same geographical area, suggesting a common founder

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Trichothiodystrophy (TTD) is a rare autosomal recessive disorder characterized by short, brittle hair with low-sulphur content. TTD patients display a wide variety of clinical features, including cutaneous, neurologic, and growth abnormalities. Common additional clinical features are ichthyosis, intellectual/developmental disabilities, decreased fertility, ocular abnormalities, short stature, and recurrent infections. Within the spectrum of the TTD-related conditions appear a number of syndromes affecting mainly organs derived from the neuroectoderm. There are both photosensitive and nonphotosensitive forms of the disorder. TTD1 (ERCC2), TTD2 or Sabinas syndrome (ERCC3/XPB gene), TTD3 or Pollitt syndrome (GTF2H5 gene), TTD4 or BIDS syndrome (MPLKIP gene), TTD5 or IBIDS syndrome (RNF113A gene), SIBIDS syndrome, and ONMRS syndrome.

We report on two unrelated patients with trichothiodystrophy type 4 (OMIM#234050) from the same geographical area, carrying the same homozygous mutation in MPLKIP gene. First patient is a 7-year-old girl, first child of healthy non-consanguineous parents (from the same town, 7000 habitants). Microcephaly (-4.74 SD), growth retardation, psychomotor delay, and brittle short growing hair. Optic microscopy showed pili torti and break stems. Homozygous c.277delT (p.Ser93Profs) mutation in MPLKIP gene was detected by exome sequencing. Patient 2 is a 2-year-old girl, second child of healthy unrelated parents, with psychomotor delay, microcephaly (-4.66 SD), limited growth and brittle hair. Hair analysis revealed trichoschisis and break stems. Due to highly concordant clinical features and geographical overlap with patient 1, analysis of Ser93Profs mutation on MPLKIP was performed first, detecting the same homozygous mutation, suggesting a founder effect in the area.

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Female patient affected by Borjeson-Forssman-Lehmann syndrome associated with a novel *PHF6* gene mutation. Ectodermal features as a hallmark for its clinical recognition.

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Borjeson-Forssman-Lehman syndrome (BFLS), caused by X-linked recessive mutations in *PHF6*, was initially described in males. Recently, de novo aberrations in *PHF6* have been identified in females with intellectual disability and a distinct phenotype including bitemporal narrowing, synophrys, dental anomalies, tapering fingers, hypoplastic nails, and linear skin hyperpigmentation.

We report on a female patient diagnosed with BFLS caused by a novel mutation in the *PHF6* gene.

Female patient aged 5 with psychomotor delay and linear skin hyperpigmentation. Second child born to healthy, and non-consanguineous parents, of Moroccan origin. Uneventful pregnancy, delivery and neonatal period. Psychomotor and language delay (IQ 74). Normal hearing. Social withdrawal and low tolerance of frustration. Brain MRI, EEG, echocardiogram, ophthalmological exam, abdominal US, skeletal survey, karyotype and fragile X analysis showed normal results. Physical exam with measurements within the normal range, sparse hair, arched eyebrows, upslanting palpebral fissures, thick lips and decayed teeth. 5th finger clinodactyly, cutaneous syndactyly of the 2nd-3rd toes, and broad first toes. Generalized nail dystrophy. Linear skin hyperpigmentation in the neck, axillae, waist and groins, with a hypopigmented patch in the abdomen.

ArrayCGH in DNA sample from skin fibroblasts, as well as *IKBKG* gene (Incontinentia Pigmenti) sequencing analysis showed normal results.

Tentative clinical diagnosis of BFLS was put forward. *PHF6* gene sequencing analysis identified a *de novo* and not previously described *nonsense* mutation (c.767C>A, p.S256X) resulting in a truncated protein.

Clinical recognition of the female phenotype of BFLS is crucial for its early diagnosis, being the linear skin hyperpigmentation together with the skeletal anomalies its most characteristic features. Its differential diagnosis includes Incontinentia Pigmenti, BAFopathies and MRX99. Its prompt diagnosis allows for offering relevant prognostic information, given the possibility of progressive multisystemic involvement (psychiatric disorders, epilepsy, thyroid dysfunction, hearing loss and retinal dystrophy among others).

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Hereditary photodermatoses by defects in the DNA repair: tumoral risk increased in childhood.

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INTRODUCTION: Hereditary photodermatoses are characterized by an increased sensitivity to sunlight caused by a DNA repair-deficiency. Most are autosomal recessive and manifest during infancy. In some cases it is linked with early development of cutaneous and internal malignancies, like Rothmund-Thomson syndrome (RTS) and Bloom syndrome (BS). We report on two patients with an earlier diagnosis.

CLINICAL CASE: 11-month-old boy, born to non-consanguineous healthy parents. Uneventful pregnancy, born at 36 weeks of gestation with birth-length 45 cm (-1.61SD) and weight according to gestational age. He presented with hypotonia, hypoplastic and proximally placed thumbs and dysmorphic facial features. Metabolic and hearing screening, cerebral and renal ultrasound, echocardiogram, brain MRI and arrayCGH were normal. He developed postnatal microcephaly and growth retardation, sparse hair and gradually appearance of cafe-au-lait and hypopigmented macules. Molecular EFTUD2 gene study was normal. Afterwards, clinical suspicion of Fanconi Anemia versus RTS established. Targeted sequencing revealed compound heterozygous c.2269C>T and c.3072_3073delAG at RECQL4, consistent with RTS diagnosis, that segregated as expected in parents.

12-month-old boy, born to consanguineous healthy parents. Pregnancy with several prenatal growth deficiency. He was born at 36 weeks of gestation with birth-weight 1350g (-3.57SD), length 41cm(-3.73SD) and microcephaly. Metabolic and hearing screening, ophthalmologic examination, renal and cerebral ultrasound were normal. Echocardiogram showed septal hypertrophic. Neonatal period was marked by feeding problems. Clinical phenotype with small size, thick lips, retrognathia, low-set ears and deep palmar creases, cafe-au-lait and hypopigmented macules. Molecular NF1 gene study was normal. Afterwards, clinical suspicion of BS established. Sequencing BLM gene revealed homozygous c.2755delC, consistent with BS diagnosis. Familiar study is ongoing.

CONCLUSION: We should consider hereditary photodermatoses in patients with pre/postnatal growth deficiency, microcephaly and skin lesions. Correlation between truncating variants in RECQL4 and presence of osteosarcoma has been reported. Clinical suspicion allows earlier diagnosis and proper medical follow-up because of multisystemic involved; tumoral surveillance and strict photoprotection.

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Rare diseases within European cross border healthcare

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Rare diseases (RD) have been for a long time neglected diseases but, at this moment, between 5000 and 8000 different rare diseases are affecting an estimated 30 million people in the European Union. European Reference Networks (ERNs) can be a solution for developing professional excellence, medical training and research, and especially, providing healthcare services to patients who have special problems and multiple needs; there are not a big amount of patients and experts either, and geographically scattered, research is fragmented, the reliable information is scarce, resources are limited, etc.

According to the European Union the health of the population is a key factor for productivity and growth but it is also a right derived directly from the principle of human rights" (This information was compiled within the framework of Research Project DER2016-76557-R: "**The Future of the Spanish social protection system: analysis of ongoing reforms and proposals to ensure their efficiency and equity (V). Health, Family and Welfare**", Project included in the 2016 call for the State Plan for R & D + I, which is aimed at the challenges of the society (2017-2019).